BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice.

Vol. XVI.—No. 176.] BALTIMORE, NOVEMBER, 1905. [Price, 25 Cents.

CONTENTS.

PAGE

The Herter Lectures. Lecture I. The Contributions of Pharmacology to Physiology. By Hans Meyer, ... 351

Observations on Several Cases of Acute Pancreatitis. By William Sydney Thayer, M. D., ... 355

Diaphragmatic Grooves on the Liver. By Robert Orton Moody, M. D., ... 364

The Rise of the Present Conceptions as to the Cause of the Heart-Beat. II. The Myogenic Theory, and Modern Studies of Rhythmicity. By E. G. Martin, ... 377

PAGE

Proceedings of Societies:

The Johns Hopkins Hospital Medical Society, ... 384

Bilateral Exostoses on the Inferior Surface of the Calcaneus, Gonorrhœal in Origin (Pododynia Gonorrhoica); Perichondritis, Probably of Gonorrhœal Origin; Bronzed Diabetes, with Enlargement of the Liver and Palpable Spleen [Dr. Barker];—Inversion of Uterus [Dr. Williams];—Thoracic Aneurisms [Dr. Baetjer].

Notes on New Books, ... 387

THE HERTER LECTURES.

Lecture I. The Contributions of Pharmacology to Physiology.[1]

By Hans Meyer,

Professor of Pharmacology in the University of Vienna.

Ladies and Gentlemen:—Before I enter upon the task for which I ask your kind attention, I desire to express my hearty thanks for the great honor you have extended to me in inviting me to deliver the Herter Lectures. The honor I accept, not so much for myself as for the science which I represent.

Experimental pharmacology is a science with essentially theoretical aims—a part of general biology, in which there is nowhere shown a greater interest than in America. I take especial pleasure in asserting that in this land of varied successes the understanding of abstract problems and of purely theoretical work thrives and ever grows, always extending to wider circles, filled with a scientific idealism which invites the most splendid and admirable sacrifices, spiritual and material. Your famous university, and indeed these lectures themselves, owe their origin to such idealistic impulses. And this gives me the courage and the desire to talk to you of The Significance and Value of Pharmacology.

It is, then, not necessary for me to claim your attention for the practical results or for their value to the practicing physician; not, however, that I undervalue this important side of pharmacology. But may I not hope at this place to be able to attain my purpose most easily, if I beg your attention to the biological results which we owe to pharmacological investigations?

For the explanation and analysis of physiological function, apart from comparative physiology, stimulation and extirpation of certain organs or parts of organs serve as general methods. Experimental physiology employed to this end mechanical and physical means almost exclusively. The scalpel and scissors, electrical, thermal, and mechanical stimuli have long served its purposes. The manifold means of chemistry have scarcely been utilized. Its appliances and its study belong, indeed, to pharmacology, which is, as an American fellow-worker has tersely said, "the experimental chemistry of protoplasm."

The drugs, that is, the chemical reagents, penetrate into the interior of the organs and reach parts which are not accessible

[1] Delivered at the Johns Hopkins Medical School, October 4, 1905.

to the scalpel and the electric current. Indeed the differential action of poisons—that which has to do with single parts of organs or single especial groups of cells—is the important part of the pharmacological method. But, we must concede that it has not attained for the most part the undoubted certainty and clearness of physiological methods, for every drug which we wish to use as an instrument of investigation must first itself be investigated, its mode of action first be recognized and determined. And you all know well how difficult and equivocal such investigations are, and it is easily intelligible that, especially in the beginnings of such investigations, while there was no large array of pharmacological facts supporting one another, one scarcely ventured from these to draw far-reaching conclusions.

An interesting example of this sort is the admirable investigation of Felice Fontana on Indian arrow poison, which was carried out more than one hundred years ago. Fontana was forced to the conclusion, through ingenious experiments, which resembled the much later ones of Claude Bernard, that the arrow poison paralyzes neither muscle itself nor the whole nerve, but only the endings of the latter and that indeed the latter must possess a structure different from the nerves themselves, of which anatomy and physiology took no cognizance. Fontana, however, did not dare to draw the right conclusion because the proof was indeed a pharmacological and not an anatomical one. Only much later was it learned that properly conducted and correctly interpreted pharmacological experimentation possesses the same power of conviction as any other exact scientific method. And it is precisely the curara poison which has led to positive physiological discoveries. By its help Boehm and Nussbaum, through the discovery of the so-called paradoxical vagus action discovered the vasopressor nerves and the accelerator fibers in the trunk of the vagus nerve in dogs and cats; and later with the help of the same poison, Boehm obtained the proof, otherwise inaccessible to physiology, that the nerve endings in the muscles possess the same capacity for fatigue and recovery as the muscle itself. The important problem of the close connection between the irritability and the conductivity of nerves was not soluble except by the aid of the pharmacological method, that is, the methodical utilization of poisons like curara, veratrin, and carbon dioxide.

Formerly it was impossible to detect any physiological or morphological difference either in the arrangement or in the general structure of centrifugal and centripetal nerve tracts. But the narcosis experiments of Fraser, Alms, Joteyko, and especially the more recent ones by Dixon with cocain, showed that they must be chemically different from one another, inasmuch as they react differently to poisons.

Highly important, also, are the physiological results which Langley obtained with the help of nicotin poisoning in relation to the sympathetic ganglia. He was able to show that by means of nicotin the sympathetic ganglia, and through them all the pre-ganglionic nerves, were paralyzed, while the post-ganglionic nerves escaped. So it is possible to decide by this means whether a nerve ends in a sympathetic ganglion or passes through it, as is the case, for example, with the trigeminus fibers through the ciliary ganglion.

The study of the action of a wholly different type of poison, namely tetanus toxin, has also furnished a series of important facts relating to the field of neuro-physiology. If one injects into an extremity of a warm-blooded animal a sterile toxin derived from tetanus bacilli, there occurs, as is well known, a local tetanus, that is to say, the inoculated limb enters into tonic extension and shows especially in the later stages of the poisoning an increased reflex irritability, while all the remaining parts of the body continue to retain their normal position and normal reflex excitability. Now it was possible to show that this remarkable phenomenon arose through the circumstance that the poison was absorbed by the adjacent motor nerve-ends and carried upward in the axis cylinder to corresponding centers of the spinal cord. The blood and lymph channels are wholly unconcerned in this transportation of the poison, and there therefore remains only the possibility that there is constantly flowing through the axis cylinder of the motor nerves a centripetal protoplasmic stream, reaching as far as the ganglia of the neurones. This was a previously unknown fact which must be of significance for the nutrition of the nerves and also for the trophic disturbances of the central ganglia which develop after section of the peripheral nerves. This is also a point which is possibly of great practical importance. In a given case of infection with the bacilli of tetanus it is permissible to assume that a direct injection of tetanus antitoxin into the main nerve of the infected area, will serve to intercept and neutralize the toxin in its passage toward the central nervous system. I have also found that such a centripetal flow of diphtheria toxin occurs in the nerves and the same thing seems to be true of certain metals which like lead, give rise to chronic neuritic palsies. Perhaps a stream of this kind passes also along the sensory nerves, but in any case its course is arrested by the spinal ganglia, so that the tetanus poison is here held fast and is unable to reach the sensory apparatus of the spinal cord. If, on the other hand, one injects the posterior nerve-roots between the root ganglion and cord, there occurs an irritation of the sensory pain-exciting apparatus in the spinal cord, and indeed without simultaneous irritation of motor or reflex structures. There thus arises the pure so-called tetanus dolorosus which is characterized by the periodical recurrence of extremely painful seizures excited apparently through the summation of minimal and ordinarily wholly inactive stimuli. It makes no difference as regards the development of the phenomenon whether the spinal ganglion has or has not been removed,—a fact which was shown by Fletcher. In this manner has arisen the proof of the existence of wholly special pain-subserving structures in the central mechanism of the spinal cord (the existence of which was long denied by French physiologists)—structures distinct from those subserving tactile and motor functions.

Finally these investigations have brought to light another

remarkable fact. In the ordinary poisoning through tetanus toxin the muscles are the seat of two distinctly different kinds of phenomena. In the first place the involved muscles become shortened without undergoing contraction in the physiological sense. This condition may exist alone. In the resting state they show neither the electrical phenomena nor the heat production nor the muscle tone that characterize a state of activity. They shorten only slowly and the affected extremity thus becomes stiff and gradually immobilized. If the muscles have not undergone maximal shortening, they are still capable of voluntary or reflex contraction, as in the case of normal muscles. It is only later that we see the well-known strychnine-like reflex tetanus in which the muscles are implicated in rapidly recurring, increasingly accentuated contractions. Since it is possible to show that both the phenomena are subserved wholly by the spinal cord, it follows that there are present in the spinal cord various structures, quite distinct from the ordinary motor mechanism, which determine the state of inactive tension of the muscles, that is to say, their length while in a state of rest. These tonus-subserving structures are not excited by other poisons, like strychnine, and we have here the fundamental distinction between strychnine poisoning and poisoning by tetanus toxin. Indeed it was only by means of the latter poison that the existence of these length-regulating tonus centers in the spinal cord was brought to light.

I have spoken hitherto of the nervous system itself, but it is true that the physiology of structures closely connected with the nervous system, as the glands, heart, blood-vessels, and muscles has been materially advanced through the use made of pharmacological agents. You are all aware of the progress in our knowledge of lymph formation and the glandular function which we owe to studies of Heidenhain; and these again were dependent in a great degree upon the help of pharmacological methods involving the application of specific chemical stimuli. I shall mention the results of some more recent investigations in this same direction in the belief that they may be less familiar to you. Very recently Wertheimer and Lepage, in Lille, reported a series of pharmacological investigations on secretion by the pancreas which led them to important results. It has long been known that the pancreas may be stimulated to secretion in a reflex manner and also, as Pawlow showed, through direct irritation of the vagus nerve. We know also as a result of Starling's work that the pancreas can be thrown into activity directly through the specific chemical stimulus furnished by the presence of secretin in the circulating blood. Now Wertheimer and Lepage were able to show that the gland has at least two distinct mechanisms through which it is possible to excite the secretion of pancreatic fluids, first, certain structures intimately connected with the vagus nerve, which may be excited by pilocarpine, physostigmine or muscarine, or completely paralyzed by atropine; and secondly, another set of structures which are not acted upon by these poisons, being neither excited nor paralyzed by them, but which react to certain other definite chemical stimuli like secretin. Possibly the latter apparatus is part of the sympathetic nervous system; at all events the case of the submaxillary gland has been brought forward by Wertheimer and Lepage as analogous since in this case the terminations of the chorda may be influenced by pilocarpine and atropine, whereas the sympathetic nervous mechanism remains intact. And, finally, just as the salivary secretion differs according as it arises through the stimulation of the chorda or of the sympathetic nervous system, so does the pancreatic secretion resulting from the pilocarpine differ from that which is obtained through the action of secretin. In the latter case the secretion contains entero-kinase, that is to say, is able to digest albumin without the addition of succus entericus.

In this connection it may be mentioned that the use of pilocarpine has led to a physiological understanding of an entirely different kind of secretion, namely, the liberation of a gas. It has long been known that the swimming bladder of fishes contains a gas, the presence of which can hardly be explained by a process of simple diffusion out of the tissues. This fact, which we owe to the observation of Huefner, led Dreser to investigate the process of liberation of oxygen into the swimming bladder of the pike, with a view to determining whether pilocarpine and other glandular stimulants gave rise to an increased accumulation. And indeed he found that when fishes were repeatedly injected with pilocarpine, the content of the swimming bladder in oxygen gas was distinctly greater than in the case of the gas from the normal fishes, which permits the conclusion that the epithelia of the swimming bladder liberate a gas in a manner analogous to the liberation of secretions from true glands, and further that these epithelia are not penetrable in either direction like a diffusing membrane.

Another fact deserves brief notice in this relation. It is the interesting observation of Magnus that when ammonia gas is injected into the veins the alveolar epithelium of the lungs is not penetrable, since no trace of ammonia can be detected in the expired air, whereas after the inhalation of ammonia the gas penetrates readily into the blood through these same epithelial cells. This is merely one striking example of the many known cases in which animal epithelial membranes are penetrable in one direction for certain substances like water, salts or urea, while opposing strong resistance to the passage of these in the opposite direction. The mechanism of this regulatory arrangement has not yet been cleared up and further progress seems hardly possible without the aid of pharmacological methods.

To enter upon the physiology of the heart at this time would carry us too far. Pharmacological facts which have proved of importance in giving us our present knowledge are doubtless sufficiently known to you. We may say, however, that even in regard to the recent controversy over the myogenic and neurogenic theories of the cardiac motions and over the general character of the heart muscle, the systematic study of the cardiac poisons has contributed much that is important

and, as Harnac has indicated, may perhaps furnish the final decision.

Permit me now to direct your attention, for a few moments, to some of the physiologico-chemical results of pharmacological investigations. It lies in the nature of things that the results should be numerous in a field that has to do solely with the chemical inter-relations between the pharmacological agent and the living organism. I shall not tire you with an enumeration of facts already well known. I shall refer only to a few of the more significant biological reactions which we owe to pharmacological investigation. The study of poisoning by acids led to the discovery of ammonia-production in the organism, and this in turn to the Schroeder experiments which positively demonstrated the production of urea in the liver. Pharmacological methods have also contributed materially to the elucidation of numerous other important problems in metabolism. One of the most actively discussed problems has been the question whether sugar can arise from proteid, and this question has been definitely answered, as it seems to me, by the experiments of Rolly. This observer conducted experiments on animals which had been rendered glycogen-free by means of fasting and strychnine spasms. He then brought about an increased destruction of proteids by means of fever, induced through the action of bacteria and toxins, and was able to demonstrate that there occurred a new production of glycogen under these circumstances in the liver and in the muscles. As the fat-reserve of the animals had already sunk to a minimum during the period of fasting, it is clear that the source of the newly-formed glycogen is to be sought in the increased destruction of proteids in the organism. The same sequence of events was demonstrated by Rolly in fasting rabbits at the time of the great destruction of proteids that immediately precedes death.

That the problem of diabetes mellitus, though still unsolved, has received light from many sides through pharmacological investigations, I need hardly state. I will merely remind you that the discovery of phlorhizin diabetes showed us a hitherto unknown capacity of the kidney to secrete sugar, that the work of Lusk and his associates led to the establishment of a definite ratio between nitrogen and dextrose excretion in diabetes, and that Blum and Herter found an adrenalin glycosuria which may perhaps throw some light on the puzzling nervous forms of diabetes.

Again, through poisoning by phosphorus and arsenic the relation of lactic and the amido-acids to the intermediary metabolism was first shown, while as regards the more intimate metabolic processes and their relation to ferment action, the toxicological experiments of Jacobi and of Wakeman have brought us important light. Through poisoning by chloral, by camphor and nitrotoluol, the discovery of glycuronic acid was made, the normal occurrence of which in the organism was only later established. Indeed the various chemical reactions of the organism, of which we have examples in the formation of hippuric acid in the kidneys, in sulphocyanide, in methylation, in oxidation and reduction, were all of them first discovered through the action of chemical or pharmacological agents. Furthermore as regards the location and intensity of these processes, the investigations of Ehrlich and of Herter have given us definite information. I would like to refer here to an interesting observation from Herter's studies which demonstrates with special clearness to the eye the oxygen requirements of the muscles and shows with what energy the muscles appropriate oxygen not only from oxyhæmoglobin, but also from other reducible substances. Herter found that if animals receive intravenous infusions of methylene blue the pectoral muscles were soon colored deep blue, but that if during the experiment the access of oxygen was hindered by giving the animals air mixed with carbon monoxid, the blue muscles in a few seconds recovered their natural red color; they had almost momentarily reduced the methylene blue to the colorless leucobase. It is also known that through the action of hydrocyanic acid the capacity of the organs to take up oxygen from the blood is much reduced or destroyed. This process also it was possible to render easily visible by the method of methylene blue infusion. As we have seen, the pharmacological method has revealed to us a series of functional characters of the organism; but its biological significance appears to extend even further. It seems possible with such methods, if only gradually, to reach a more intimate knowledge of the chemical constitution of protoplasm, and finally, perhaps, to arrive at an insight into the chemical interpretation of its functions. If, under the influence of a pharmacological agent, we observe an immediate essential alteration in the function of a cell, we have to assume that a chemical change has occurred in its vital center—in what Ehrlich has called the "Leistungskern," that is, the chemical center of vital activity. On the other hand if we have before us a gradually developing alteration, this may have been called forth in a secondary manner, through chemical changes in the reserve material or in the supporting elements of the cells, perhaps in the groups of atoms which we conceive as side-chains. Given a knowledge of the constitution and the chemical mode of action of agents operating as acute intoxicants, we should also be able to reach conclusions as to the chemistry of their point of attack, that is to say, regarding that substratum of the living substance which corresponds to the chemical constitution and action of the poison. With a similar idea in mind Oscar Loew, twenty years ago, considered himself justified in assuming the presence of an aldehyde group in the living protoplasm, basing this view on a series of merely qualitative toxic reactions like those obtainable by hydroxylamine, diamid, and other substances.

An example of another pharmacological method which may, perhaps, prove of utility is the investigation of the narcotics. The quantitative comparison of the action of aliphatic narcotics (alcohol, ether, chloroform, etc.) leads to what I believe to be the unavoidable conclusion that certain fat-like substances like lecethin must be conceived as constituting integral parts of the "Leistungskern." It happens that one can compare with considerable exactitude in a quantitative way, the efficacy of this numerous group of bodies.

This comparison has brought out the fact that the degree of activity is approximately proportional to the individual chemico-physical affinities of all these substances, that is, their solution-tensions for fat-like bodies compared with their solution-tensions for watery media. From this almost rigid parallelism it follows with a high degree of probability that in the union of ether, chloroform, etc., to a fat-like substance—a lipoid—we have the origin of the narcosis of the cell; in other words the lipoid belongs to the essential functionally active constituents of the cell. It has been urged against this conclusion that the cell lipoids occasion merely a stronger or weaker accumulation of the narcotic which then acts on the true albuminoid life-center of the cell in proportion to the degree of this accumulation. There are, in reality, only two possibilities. First, one may assume that the narcotic operates only through its presence in lifeless lipoids, whence it acts from a distance, perhaps through a sort of induction, upon the living cell-center itself without entering into reciprocal chemical action with the center. Such a view could be neither refuted nor established. But in order to explain the above-mentioned parallelism, it would be necessary on this supposition to invoke the aid of the very improbable hypothesis that all the different narcotic substances compared on an equimolecular basis, exert an equally strong induction. But this hypothesis wholly fails to allow for the different influence of special groups of atoms, as, for example, the ethyl group, the methyl group, etc. Hence it is clear that such an action at a distance must remain problematical, and furnishes us no actual explanation. On the other hand, we may make the much more likely assumption that the narcotic substance enters into a reciprocal, reversible, chemico-physical action with some constituent of the "Leistungskern" or "life-center," the strength of which reaction is dependent on the intensity of this reciprocal action. Then again, the law of mass action here comes into play, that is the law of distribution. We may even leave the lipoid for the moment out of account. In this case it would have to be regarded simply as an intermediary solvent and would remain without influence upon the equilibrium established by the narcotic between the blood and lymph plasma on the one hand and the "Leistungskern" or "life-center" on the other. Experiment, however, showed that the affinity of the living cell substance for a narcotic, measured by the observed intensity of action, runs parallel to the experimentally observed fat affinity of the narcotic, or, in other words, that the unknown constituent of the living cell or "Leistungskern" must itself possess certain properties of a fatty substance, or, in short, must itself be a fat-like or lipoid body. And thus we come back to the very conclusion of which I have already spoken. I have expressed myself in somewhat greater detail than is perhaps warranted by the importance of the question. I have, however, thought such a critical discussion of the problem of some interest as it seems of fundamental significance for the evaluation of a pharmacological analysis of this kind.

I have already said that perhaps the highest result of pharmacological investigation may prove to be the winning of an insight into the chemical nature of life processes themselves; indeed, the first important ground in this direction has already been won. You are all familiar with the important investigations of Jacques Loeb, to whom we owe a knowledge of the essential significance of the individual metallic ions, for the general life processes. But what is still more important, Loeb has succeeded in inducing very special biological reactions as the effect of chemical action. He has shown that heliotropism can be excited by definite chemical reagents such as carbon dioxide and other substances, instead of through the action of light, which is a contribution to the understanding of the mechanism of this singular reflex function. Finally, he has shown that through certain definite chemical procedures like the action of hypertonic salt solutions, combined with ethyl acetate, the unfructified eggs of sea-urchins may be stimulated to parthenogenetic normal development, an observation which may prove of great significance for the understanding of the process of fertilization.

And with the mention of this admirable investigation, permit me to close my address of to-day.

OBSERVATIONS ON SEVERAL CASES OF ACUTE PANCREATITIS.

By WILLIAM SYDNEY THAYER, M. D.,

Professor of Clinical Medicine in the Johns Hopkins University.

The following cases, four of which come under the head of suppurative, and one of gangrenous pancreatitis, are deemed worthy of report, as well from a diagnostic standpoint as from the fact that their course and outcome emphasize the importance of early recognition and prompt surgical interference under similar circumstances. The first of these cases was seen a few months ago in consultation with Dr. J. C. Pound. The other four are from the wards of the Johns Hopkins Hospital. Three of these I have had the good fortune to see myself; one was under the care of Dr. Futcher.

CASE I. *Woman; 51. Previous attacks of biliary colic. Onset of present illness with an attack of biliary colic and jaundice followed by fever, nausea, vomiting, and pain on the left side of the abdomen. Deep tumor mass occupying the epigastrium and left side of the abdomen, extending well out-*

ward and backward into the flank. Operation, thirty-seven days after onset, revealed parapancreatic abscess with disseminated fat necrosis. Recovery.

Mrs. W., married, 51 years of age, was seen in consultation with Dr. J. C. Pound on 31 October, 1904. The *family history* was negative. She had had typhoid fever in childhood but had otherwise been a healthy woman. Married; no children. Passed the menopause a year ago. Ten years ago had a few attacks of sharp pain in the epigastrium and right hypochondrium seldom associated with nausea or vomiting.

Present Illness.—In June she had had a sharp attack of pain in the epigastrium and right hypochondrium lasting several days; this was associated with jaundice which lasted a week. The stools, for several days, resembled putty. Four weeks ago to-morrow the patient had another attack of pain in the epigastrium of not very marked severity, though it was enough to require an hypodermic of morphia. This was followed by jaundice which lasted four or five days. There was also fever and nausea and vomiting which, at first, were rather severe. There was what she calls a "sore pain" in the epigastrium, particularly on the left side. The nausea and vomiting, worse in the afternoon, have continued off and on ever since. There has been intermittent fever associated with considerable sweating at times, especially at night. The main complaint has been of a "sore pain" throughout the left side of the abdomen.

On *physical examination* the patient was found to be a well-nourished woman of a rather sallow, yellowish appearance, suggesting suppuration; temperature 102.8°. The thorax was clear throughout, the *lungs* descending behind to an equal level on both sides. The *heart* sounds were clear; the apex in normal position. The *abdomen* was rather full, slightly more prominent on the left side, especially a little above the crest of the ileum. On palpation there was to be felt a deep mass extending somewhat across the epigastrium to the right but especially filling up the left side of the epigastrium, and extending downward to a point as low as the level of the anterior superior spine of the ileum. On the left it reached to a point about as far out as the mid-axillary line. It was deeply situated below the gut. The border of the *liver* was not clearly felt and on the right did not, apparently, descend below the costal margin. The mass suggested to Dr. Pound and myself a deep parapancreatic abscess, although the situation was much further to the left than is common in such cases. The relation of the symptoms to the attack of biliary colic was, however, suggestive.

1 November. Examination of the blood showed: red blood corpuscles, 3,964,000 to the cu. mm.; colorless corpuscles, 16,800 to the cu. mm.; hæmoglobin (Dare) 61%.

A differential count of 500 leucocytes stained by Ehrlich's method showed: small mononuclears, 8.6%; large mononuclears and transitionals, 6.6%; polymorphonuclear neutrophiles, 84.4%; eosinophiles, 0.4%; mast cells, 0.4%.

The red cells were normal in size and form. There were no irregularities in contour; no nucleated red corpuscles were observed.

Urine.—Normal, amber color, clear, acid 1009, no albumin, no sugar. Microscopically, few squamous epithelial cells; an occasional leucocyte; no casts; no crystals.

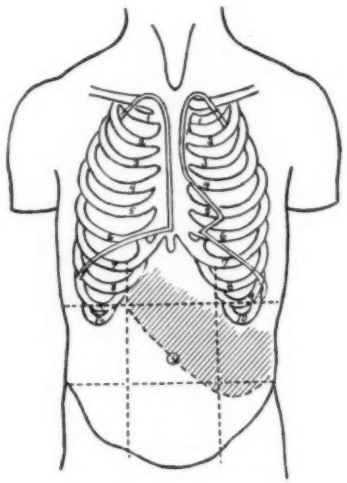
An exploratory operation was suggested, but the family demurred.

7 November. On this date the patient was again seen in consultation with Dr. Pound. During the past week the condition has not essentially changed. Examination to-day, however, shows some slight modification in the character of the mass which extends, perhaps, a little lower, while it is not as prominent in the epigastrium. There is, also, flatness in the left back, reaching to a point as high as the angle of the scapula. The upper limit of dulness is higher in the scapular line than at the spine. In front, however, the lower level of the lung is about at the same point as on the right. Below the line of flatness, vocal fremitus is absent, while the respiration is rather indistinct, of a tubular quality, with nasal voice sounds, somewhat suggestive of ægophony, especially toward the upper part.

9 November. The patient who had been urged to consent to operation, agreed to see Dr. Finney to-day. On examination a decided change was noticed in the outline of the deep mass, in that it projected much more in the flank, reached further outward and began to show distinct evidence of fluctuation. There was also slight œdema of the subcutaneous tissue just above the crest of the ileum.

The patient was removed to the Union Protestant Infirmary where Dr. Finney operated on the following day.

The abscess was opened in the left flank where it appeared to be pointing. This opening led into a very large cavity which extended upwards into the epigastrium in the region of the pancreas, downwards toward the pelvis and backwards into the para-renal region. Escaping with the pus were masses of necrotic fat and shreds of necrotic tissue.



Position of deep mass in Case I.

The patient bore the operation well, but the fever, ranging from normal in the morning to 100° and 101° at night, continued. There were frequent attacks of nausea and vomiting; little food could be retained. On 20 November, I saw the patient who was much emaciated, extremely feeble and delirious. The pulse was 140. The condition was such that it was feared she might not live through the night. From this time on, however, she steadily improved. The vomiting ceased, the appetite returned and the delirium disappeared.

On 22 December, the patient had so far improved that she was able to go home, although the evening temperature was still a little above 99° while a sinus persisted.

The *urine* was free from sugar throughout.

In the discharge from the wound large masses of necrotic tissue appeared on various occasions. On 20 November, for instance, a piece measuring 6 x 6.5 cm. escaped, while on 29 November, a piece was discharged as large as the palm of the hand.

Several of these masses suggested bits of true pancreatic tissue.

A specimen was sent to Dr. Bloodgood who made the following report:

Pathological No. 5897. Mrs. W., patient of Dr. Finney, U. P. I.

"*Clinical Diagnosis, Pancreatic Abscess.*—Necrotic and hæmorrhagic tissue shows no evidence of remains of pancreatic gland.

Gross Description.—The specimen consists of a mass of tissue which is so friable and mushy that it cannot be handled without falling to pieces. It is of a greyish pink color and seems to be somewhat loosely bound together by fibrous shreds; in one area there is a blackish mass, quite friable, which has the appearance of a blood clot. . . . .

Microscopical Description.—Section 1, marked 'blood clot,' shows areas of disorganized blood in a granular tissue taking the eosin stain in which I can recognize no stained nuclei. The architecture of the necrotic tissue suggests fat.

Section 2, marked 'tissue' has the same appearance as section 1, no nuclei taking the stain. There is no tissue suggesting the architecture of fat and no positive evidence of pancreatic tissue.

Remarks.—Clinically, the case was considered by Dr. Thayer to be one of pancreatic disease. The tissue sent to the laboratory was of necrotic hæmorrhagic fat which came from the abscess cavity."

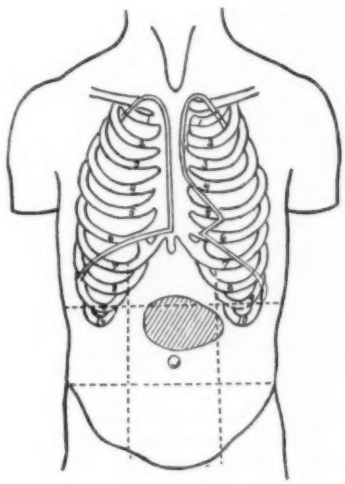
CASE II.[1] *Man; 34. For a year and a half attacks of cramp-like epigastric pain; present attack: severe epigastric pain; vomiting; fever; epigastric tumor; diagnosis of acute pancreatitis with parapancreatic abscess; operation twelve days after onset; recovery.*

Hosp. No. 10,210; Surg. No. 3190. W. E. D.; aged 34; married; a piano polisher, was admitted to the Johns Hopkins Hospital on 25 June, 1905. *Family history*, negative. *Previous History.*—As a child had had chicken pox and pneumonia, the latter at the age of six. Had been married thirteen years; no children. For years had been a regular drinker of beer and whiskey though not to great excess. Smoked and chewed tobacco. Five years before entry had been overcome by heat. Was in bed at this time for a week. For two years had been subject to attacks of nausea in the morning with occasional attacks of vomiting, the vomitus consisting of a greenish, slimy substance.

For a year and a half the patient had been subject to attacks of severe cramp-like pain in the abdomen. The pains were localized in the median line across the epigastrium and about the umbilicus. The first attack came on at night and was very severe, so much so that relief was obtained only by large doses of morphia. With each attack the patient had been compelled to remain at home for from several days to a week. There was often vomiting; probably fever; never jaundice.

P. I.—Ten days before entry the patient came home from work on account of a slight sensation of heaviness in the epigastrium and a feeling of anxiety similar to that which had preceded his other attacks of pain. The same evening vomiting came on. The pain was intense and continuous, and a swelling appeared just above the umbilicus at the area of greatest tenderness. There was constipation. During the next week the patient was obliged to remain in bed. There was continuous fever, and delirium. A diagnosis of abscess of the liver was made by his physician. On 25 June, he was admitted to the Johns Hopkins Hospital. I saw the patient shortly after entry and made the following note:

"On physical examination the patient is a well-formed man, quite corpulent; lips and mucous membranes of good color. The tongue is coated, the temperature elevated; the mental condition dull; the patient is a little confused. Examination of the *thorax* is negative. On inspection the *abdomen* is full, showing a rather undue prominence in the median line across the epigastrium. Hepatic flatness begins at the sixth rib in the mamillary line, while in the same line the lower border of the liver can, apparently, be felt about on a level with the umbilicus; it is not, however, very distinct, owing to the tension of the abdominal muscles. Liver-flatness is coextensive with this area. Passing toward the median line the resonance becomes tympanitic. Just below the xyphoid cartilage the resonance is loudly tympanitic, and from the sensation conveyed by palpation there is evidently an air-containing organ (stomach?) just below the skin. Below, between this and the umbilicus, at the point of maximum prominence, is to be felt a deeply seated mass, over which there is well marked tympany. The outline of the mass is indistinct. It is not tender on ordinary palpation. To the right this mass is not to be sharply separated from what would appear to be the liver; to the left it reaches about to the costal region. Pressure over the lower left ribs does not cause pain. In the knee-elbow position nothing further is to be made out. *Splenic* dulness is



Position of the palpable mass in Case II.

about normal in area, and does not pass the costo-articular line. There are no glandular enlargements." The appended chart, made at the time of this examination, shows the position of the deep mass, of the hepatic dulness, and the epigastric tympany.

The *urine* was free from albumin or sugar.

The *blood* showed a leucocytosis.

A diagnosis of acute pancreatitis with disseminated fat necrosis and, possibly, sequestration of the pancreas was made, and an exploratory operation was advised. This was performed by Dr. Finney on 27 June.

In the median line, adjoining the liver and stomach, a mass of adherent fatty tissue was found which was filled with numerous fat necroses. This mass of tissue was adherent to the stomach and liver. The transverse colon passed over the lower part of the opening and was involved in the adhesions. The general abdominal cavity was packed off with gauze and an opening into the mass was made later. From this opening a large quantity of brownish pus with large masses and shreds of necrotic fat escaped. The finger passed far backward at the bottom of the wound into what appeared to be a cavity in the pancreas. The main excavation represented evidently the lesser peritoneal cavity. The material discharged from the opening showed pus, bacteria, numerous fatty acid crystals and large and small masses of

[1] Published previously in the Am. J. M. Sc., Phila, 1895, CX, 396.

necrotic fat. Cultures were unfortunately not made, as the opening occurred unexpectedly. No tissue that could be definitely identified as pancreatic was found in the discharge. The patient made a perfect recovery and has been well ever since. His present good health may be inferred from his appearance, for he has kindly consented to come before us this evening.

CASE III.[2] *Man, 47; six months before attack, jaundice with biliary colic; present illness: sudden intense cramp-like abdominal pain; nausea; vomiting; collapse; abdominal distension; constipation; tender, painful tumor in the right half of epigastrium and hypochondrium; diagnosis by Dr. Bloodgood of pancreatitis; operation on 21st day; death; necropsy; necrosis of pancreas; suppurative parapancreatitis; stone lodged in diverticulum of Vater.*

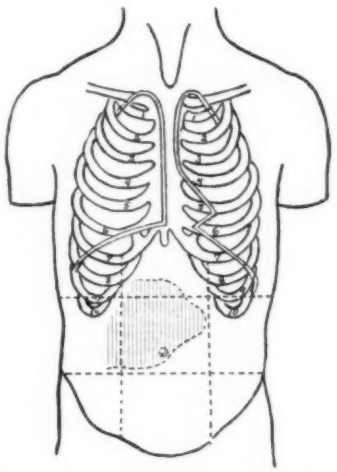
Hosp. No. 30,996; Med. No. 11,482. J. T. H.; 47; married; physician; entered the hospital on 26 June, 1900, complaining of abdominal pain, distension and fever.

The *family history* was negative. *Previous History.*—Has had scarlet fever and measles. Chews tobacco; does not smoke or drink; is not a heavy eater. Has complained frequently of pain and distension after eating; rarely, nausea and vomiting.

Six months ago, had an attack of jaundice accompanied by slight pain in the abdomen; the jaundice lasted for several weeks. During this period the stools were but slightly clay-colored. His sister is inclined to believe that this attack was not dissimilar to his present illness. There was some nausea and a good deal of abdominal pain; moderate fever. He was obliged to stay in bed for some time, but by the end of three weeks had recovered entirely.

Present Illness.—Eighteen days ago, at nine o'clock at night, there was a sudden attack of nausea and vomiting with intense cramp-like abdominal pains which could not be localized. The patient was collapsed, the abdomen distended, and the pain rather general; no change in the condition for four or five days. On the third day the patient was found to have a temperature of about 101.5°. After the first night the vomiting became less frequent though it has occurred off and on ever since. The bowels were constipated, possibly due to the morphia which was given; the skin, cold and clammy. The respirations were not accelerated. On about the seventh day a tender area was noticed in the right hypochondrium which was a little fuller than any other part of the abdomen, though at no time during the illness were the muscles of the right side more rigid than those of the left. The physician believes that the abdominal respiratory movements were practically normal. On the fifth day the bowels were opened by purgatives. The fæces were normal in color and have been essentially natural since then, although laxatives have had to be used twice. The last movement occurred four days ago. For eleven days there has been an irregular fever ranging between 101° and 103°; there have been four or five chills. Nausea and vomiting have been slight and the abdominal pain has not been severe. But little morphia has been given. The area of tenderness in the right hypochondrium has, however, persisted, while the abdominal distension has steadily increased. There have been no cerebral symptoms, and the mind has been perfectly clear throughout. There has been no jaundice. The patient has lain on his right side during most of the time, with the thighs flexed on the abdomen. The pulse has ranged from 100-120; at times, dicrotic.

26 July, 1900. On entrance, the patient was seen by Dr. Futcher who made the following note: "The patient is a man of large frame; complexion, a trifle sallow; mucous membranes, somewhat anæmic; tongue, a little coated; very slight yellowish cast to the conjunctivæ. He lies upon his right side with the knees flexed. The pulse is of fairly good volume and tension, regular in force and rhythm, vessel wall not thickened. *Lungs*, clear throughout on percussion and auscultation. *Heart.*—Point of maximum impulse not seen or felt. Sounds best heard in the fourth interspace, 9 cm. from the midsternal line; sounds enfeebled at apex and base. *Abdomen.*—The right costal groove is partially obliterated; the right lumbar region slightly fuller than the left. There is a distinct, visible prominence in the right hypochondrium and the right half of the epigastrium, extending into the upper right quadrant of the umbilical region. Distinct pulsation is visible in the upper epigastrium. Respiratory movements are less marked on the right than on the left. On palpation there is a distinct resistance in the area above noted. The lower margin of this area of definite resistance corresponds with the line indicated in the chart extending a little to the right of the umbilicus to a point about on a level with the anterior



Position of palpable mass in Case III.

superior spine, passing up through the umbilicus, the left border of the umbilical region and around again through the epigastrium to the right. To the right the outline of the mass is not so easily felt. The margin is rather round and extends to a point 10.5 cm. below the costal margin in the mamillary line and to the level of the umbilicus in the median line.

The surface is firm, a little irregular. The lower margin descends on inspiration. In the median line the fingers can be pressed in above the resisting mass. There is dull tympany over the tumor and the dulness is continuous above the costal margin with the hepatic flatness which extends to the middle of the sixth interspace. . . . The border of the spleen is not definitely felt. There is nothing to be made out in the right iliac fossa." Leucocytes 18,300.

27 June, 1900. The stool passed last night was soft, unformed, golden in color throughout, rather resembling gold dust and having a definite glistening appearance. There was nothing remarkable save for the large number of fatty acid crystals.

Following inflation of the stomach with tartaric acid and bicarbonate of soda, the epigastrium and upper part of the umbilical region became decidedly more prominent. There was no peristalsis. The upper border of the stomach tympany began over the middle of the sixth interspace in the parasternal line

[2] This case has been reported by Dr. Opie in Am. J. M. Sc., 1901, CXXI, 27.

and reached a point 5.5 cm. above the level of the umbilicus in the median line. The stomach, after inflation, measured only 21 x 11 cm. The mass in the right hypochondrium and right half of the umbilical region did not appear to be connected with the stomach. The glands in the left axilla were slightly enlarged. Leucocytes, at 11 a. m., 19,300. The condition was about the same. There was some nausea and vomiting early in the morning. The vomitus was green in color, acid to litmus. Free hydrochloric acid was present, the acidity amounting to 27; total acidity, 50.

Urine.—High; clear; acid; 1017; no sugar; trace of albumin. Microscopically: mucous cylindroids; one granular cast seen.

28 June, 1900. Leucocytes, at 4 p. m., 19,500. There has been no change in patient's condition. He takes his nourishment well and has not vomited since yesterday. The temperature, since admission, has ranged between 99.2° and 101.8° and but once has been above 100.4°. He has complained of no pain and there is but little sensitiveness on palpation over the mass. The patient has, at times, been somewhat irrational and very drowsy. The right lateral decubitus and the flexion of the knees and thighs continues. There is no muscle spasm. The pulse has varied from 108-124, and has, at times, been irregular and intermittent. The respirations since admission have been from 20-28 to the minute. A fresh specimen of blood shows nothing abnormal save a leucocytosis, chiefly polymorphonuclear.

29 June. 6 a. m., leucocytes, 18,500. Last night the patient was decidedly irrational; the pulse, irregular and rapid. There was marked restlessness, the patient endeavoring to get out of bed. The temperature rose during the night reaching 104° at six this morning. Stool, obtained by rectal tube, showed no amœbæ; no red blood corpuscles; no pus. Color, light yellow; a few fatty acid crystals. The stool early this morning was liquid, of a yellow ochre color; no amœbæ; no blood corpuscles; no pus. There was a large quantity of fatty acid crystals; no fat globules.

Dr. Futcher made the following note: "The mass in the right hypochondrium and epigastrium has not apparently changed in size. There is no tenderness on palpation." The temperature rose at six p. m. to 104°. The *urine*, throughout, was free from sugar.

The patient was seen on this date, by Dr. Bloodgood, who made a diagnosis of suppurative pancreatitis and advised operation which was performed on the following day. On opening the peritoneal cavity numerous areas of fat necrosis were visible. The omentum was matted together. On making an opening through the omentum a large amount of dark, brownish black fluid escaped. The patient's condition was so bad that a drainage tube was inserted and the wound closed without further investigation. The general weakness, however, increased and at 8 p. m. the patient died.

Necropsy.—Anatomical diagnosis; cholelithiasis; calculus lodged in the common duct near its orifice; slight jaundice; old hæmorrhage within and about the pancreas; localized necrosis of pancreas; chronic interstitial pancreatitis; necrosis of fat of pancreas; greater and lesser omentum, mesentery and subperitoneal tissue of the abdominal wall; parapancreatic abscess limited by lesser peritoneal cavity; laparotomy wound.

A partial necropsy was made by Dr. Opie through the incision three hours after death. "The body is that of a large-framed, muscular man with abundant subcutaneous fat. *Peritoneal Cavity.*—The omentum, which contains a large quantity of fat, is adherent in the neighborhood of the operation wound to the anterior abdominal wall by light, fibrinous adhesions. Its surface is thickly studded with conspicuous, opaque, white areas, varying in size and shape, but usually round and about 3 mm. in diameter, extending about 1.5 mm. below the surface. On section similar foci are found embedded in the fat. Opaque, white areas are present in the fat of the mesentery, where they are most abundant near its intestinal margin, in the subperitoneal fat of the anterior abdominal wall, over the bladder, over the kidneys, and about the colon. *Abscess cavity.*—The drainage-tube inserted into the abdominal wound passes through a small, incised opening in the great omentum and enters an immense abscess cavity which occupies approximately the site of the lesser peritoneal cavity. The foramen of Winslow is closed. The stomach is pushed upward and forward, and its anterior surface is adherent to the lower surface of the liver to the left of the gall-bladder. The spleen, partially surrounded by fat containing many opaque, white areas, is bound by fibrous adhesions to the diaphragm. The walls of the cavity are very irregular and ragged, and have a necrotic appearance, in general opaque and gray, occasionally black. This blackish-gray appearance extends only a short distance below the surface, and where the wall is formed by fat, give place to numerous foci of opaque, white color. The retroperitoneal fat in front of the left kidney and psoas muscle has been eroded, and an extension of the cavity passes behind the jejunum near its junction with the duodenum. To the left of the descending portion of the duodenum, occupying the position of the pancreas and projecting forward into the abscess cavity, is a great mass of black material, necrotic in appearance, extending to the left as far as the spleen. This material is reddish-black on section, somewhat spongy in texture, soft, dry, and friable. The cavity contains a large quantity—at least 500 cc.—of fluid, reddish gray material, containing fat droplets and black, necrotic particles. . . . . The *bile ducts* are slightly dilated and contain thin yellow bile. The *gall bladder* is bound by numerous adhesions to the duodenum and stomach. Its walls are thickened and it is much distended, containing viscid yellow bile and a large number—over one hundred—of brown facetted calculi varying in diameter from 0.5 to 1 cm. The hepatic, cystic and common ducts are much dilated. On opening the duodenum a stone is felt below the mucous membrane situated in the common bile duct, about 1.5 cm. from the orifice of the diverticulum of Vater. It is 7 mm. in diameter and resembles those present in the gall bladder.

Pancreas.—The pancreatic duct unites with the common bile duct at a point 7 mm. from the duodenal orifice. For a distance of 1.5 cm. the two ducts are separated by a thin septum only, and in contact with this septum is lodged the gall stone previously mentioned. The pancreatic duct is not distended. The pancreas occupies the posterior wall of the lesser peritoneal abscess cavity, and is covered by the mass of reddish black, friable material, changed, coagulated blood, above described. The organ is of large size, and the glandular tissue is in great part firm, yellowish-white, and well preserved. The interstitial tissue has a dull, reddish, in places hemorrhagic appearance, and contains conspicuous, opaque, areas of irregular shape. Where the anterior surface of the head and body is in contact with the overlying material there is a superficial zone of soft, grayish, necrotic appearance.

The other organs—*heart, lungs, spleen, stomach, intestines,* and *kidneys*—present no noteworthy alteration. . . . "

The complete histological examination may be found in Dr. Opie's article above referred to.

Bacteriologically, cultures from the heart's blood, lungs and liver showed *bacillus coli.* A plate culture from the material covering the pancreas and forming part of the abscess wall contained the *B. coli* and the *B. lactis aërogenes* and the *B. proteus.*

CASE IV. *Woman; 49. Previous attacks of biliary colic; sudden severe epigastric pain relieved by morphia; persistent dull epigastric pain with nausea and vomiting; tender tumor in the right umbilical, epigastric and lateral abdominal re-*

gions; diagnosis by Dr. Halsted of pancreatitis; operation; recovery.

Hosp. No. 39,822; Med. No. 14,390; Surg. No. 13,415. V. C. B.; single; 49; housekeeper; a patient of Dr. J. T. Strickland of Roanoke, Va., was admitted on 20 May, 1902, complaining of "stomach trouble."

Family history.—Negative. *Previous history.*—Patient has had measles, chicken pox, and whooping cough and, fifteen years ago, typhoid fever. Passed menopause five years ago. Has been subject to severe headaches; has never suffered from digestive disturbances until four years ago when she was suddenly seized with an agonizing pain in the pit of her stomach; the pain did not radiate; it continued until relieved by morphia. There was no nausea or vomiting but she felt cold and sweated profusely; no jaundice. From that time she has had occasional similar attacks but they have not increased in frequency in the past year, and she has always recovered on the following day.

Present illness.—Five weeks ago the patient had a sense of discomfort in the epigastrium after eating supper; this distress became gradually worse, and, in about four hours, had developed into an agonizing pain in the pit of the stomach. The pain did not radiate into the back. She was cold; there was a drenching sweat but no nausea or vomiting; no jaundice. Hot applications gave no relief, which was afforded only by an hypodermic injection of morphia. The attack was similar to those which she had had previously, but more severe. Ever since this time she has felt very ill. There has been constant dull pain in the epigastrium; attacks of vomiting, persistent and protracted, have recurred every two or three days, the vomitus being thick and dark green in color. She has been able to take only very light food. At the onset there was obstinate constipation for about a week; thinks she has had a little fever every now and then toward night. There have been no chills; no sweating at night. There has been no attack of sharp pain since the onset. About three weeks ago she noticed a hard tender mass in the abdomen which has not disappeared. She has never been jaundiced; has been extremely nervous and has not slept well.

On the day of entry the blood count showed: red blood corpuscles, 4,120,000 to the cu. mm.; colorless corpuscles, 8250 to the cu. mm.; hæmoglobin, 68%.

On the same day the following note was made by Dr. Thayer: "The patient is sparely nourished; lips and mucous membranes of good color; the skin is slightly yellow; the sclera pure white. The temperature last night was 100.5°, this morning 99.2°. Pulse 31 to the quarter, of moderate size, fairly good tension; vessel wall, not palpable.

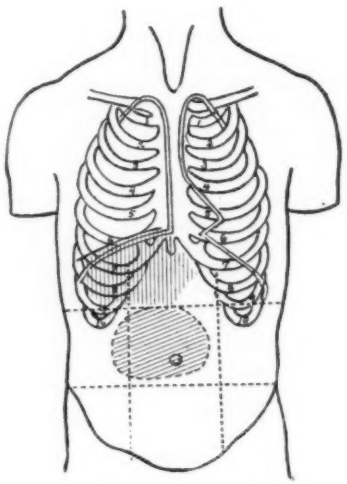
Thorax symmetrical; costal angle about 90. Expansion equal. Resonance clear in fronts and axillæ. *Heart.*—Apex impulse in the fifth space in normal position; sounds clear, of normal relative intensity.

The *abdomen* looks a trifle fuller in the right epigastric and umbilical regions than on the left. No observable peristalsis. On palpation, there is to be felt a firm, very tender mass which lies in the epigastric and right umbilical regions extending over into the right lateral abdominal region. This descends to a point slightly below the level of the umbilicus and moves downward slightly with inspiration. It has, so far as can be made out, no sharp border. To the right the outline is indistinctly to be felt passing a little beyond the vertical line extending through the anterior superior spine of the ileum. To the left it reaches apparently about 3-4 cm. beyond the umbilicus. The hepatic flatness passes directly into the dulness over the mass but the dulness is not absolute. Even on light percussion there is slight tympany over the tender area. The spleen is not palpable though there is dulness to the costal margin as indicated on the chart. The border of the mass has not the sharp edge of the ordinary hepatic border though it does feel rather firm. There is no apparent fluctuation. Below this area the abdomen is negative. There is no prominence in the right lumbar region. The tumor mass is not to be felt with the posterior hand over the lower ribs. Without dilatation it is impossible to differentiate the stomach from the other air-containing organs. As the patient changes position the tumor is practically immobile, falling but little toward the dependent side."

The *urine* was of normal color; acid; 1017; no sugar; trace of albumin. Sediment, flocculent containing a few hyaline casts, mucous cylindroids and epithelial cells. No Diazo reaction. The Widal test was negative.

The temperature during the two days that she was on the medical side, ranged between 99.2° and 100.2°. Nothing remarkable was noted about the character of the *fæces*, no entry being made in the history.

On the following day the patient was seen by Dr. Halsted who regarded the case as one of pancreatitis and advised operation, which was performed by him on 23 April. An incision was



Position of tumor in Case IV.

made over the mass in the right hypochondrium, through the rectus muscle and separating the fibers. When the peritoneum was reached there were some œdema and evidence of inflammation. The peritoneum was divided and the abscess cavity was immediately encountered, from which about an ounce of thick, yellow material was evacuated. This was odorless and contained numerous small masses resembling fat. The opening was enlarged a little and the cavity explored. It ran downward for a distance of about 7 cm. and backwards perhaps 10 cm. It appeared to be lined on the sides by bowel and posteriorly by a hard mass, the exact position of which could not be determined. The abscess cavity contained masses of necrotic looking tissue which Dr. Opie regarded as necrotic omental fat. A considerable quantity of this necrotic stringy material was evacuated and the abscess cavity was wiped out and packed with iodoform gauze. . . . The abdominal cavity was not opened and no exploration was made to determine the presence or absence of gall stones. The patient made an uninterrupted recovery and was discharged from the hospital on 24 June well.

Case V. *Man; 37. Seven months before entry, intense epigastric pain; vomiting and purging; gradual recovery in*

two months; three weeks before entry, epigastric pain; vomiting; persistence of symptoms in a milder degree; diagnosis of pancreatitis; operation; death from hæmorrhage into cavity; necropsy: gangrenous pancreatitis; perforation of stomach and duodenum.

Hosp. No. 43,308; Med. No. 15,860; Surg. No. 14,924. S. T. H., married, 37 years old, mechanic, patient of Dr. Jones of Newbern, N. C., was admitted on 7 July, 1903, complaining of pain in the stomach, nausea and occasional vomiting.

The *family history* was negative. *Personal history.*—The patient had chicken pox at 9, measles and whooping cough at 10; malarial fever at 24; occasional attacks of "kidney colic." He was married at 31. His wife had had no children and no miscarriages. Had been a hard worker, his occupation keeping him indoors most of the time. Had not been a heavy drinker but occasionally drank apple brandy. Had been a hearty eater; a slight smoker; had chewed a good deal of tobacco; denied venereal disease.

Present illness.—Seven months before entry he was seized at night with a sudden severe pain in his stomach associated with vomiting. The pain which had improved, returned in the morning and continued most of the day associated with moderate purging. The vomitus contained no blood. The pain lasted off and on for two months but finally entirely disappeared. His health remained fair up to three weeks ago, when he had another attack of pain in the stomach associated with sweating and moderate vomiting. There was no jaundice; he was somewhat constipated. The bowels were moved by purgatives. He had weighed 185 pounds, but lost much with his first attack after which, however, his weight returned to 172 pounds. It now is about 160. During the last three weeks he has grown much weaker. At one time a tumor is said to have appeared in the gall bladder region which was lifted by the heart beat and pulsated. It has, since then, disappeared entirely. On the day of entry the following note was made by Dr. Thayer: "Complexion very sallow, conjunctivæ clear, slightly, if at all, yellow. Tongue, dry with a yellowish coat; clear and pale on the edges. Complexion, very dark. Patient looks ill; the eyes are sunken; pulse 29 to the quarter at the beginning of examination; size moderate, rather compressible.

Thorax.—Symmetrical; costal angle, 90. Note over the right lung seems slightly more tympanitic than over the left. Flatness begins on the right side at the sixth rib in the mamillary line; on the left at the lower border of the seventh. Respiration is clear in the left front and axilla; also in the right front. The lower border of the left lung behind is a trifle lower than that of the right. Back is clear on auscultation.

Heart.—Negative. *Abdomen.*—Natural. Well marked epigastric pulsation. The left side of the epigastrium is slightly fuller than the right. On palpation there is to be felt a distinct muscular resistance in the epigastrium more particularly on the right side. The *liver* is rather indistinctly felt. It descends on deep inspiration, from under the ribs, in the anterior axillary line. Under the superior belly of the right rectus there seems to be something which descends with inspiration but the tenseness of the muscle prevents accurate palpation. In the median line also there is a distinct tenderness but nothing very definite is to be felt. The gastric resonance is easily made out extending rather far to the right and lying rather transversely. The *spleen* is not distinctly palpable though the dulness just passes the costo-articular line. In the median line the liver dulness reaches one and a half finger's breadths below the tip of the ensiform.

A little later Dr. Cole observed that the patient looked very ill and was in a rather collapsed condition. The abdomen was a little full, especially in the upper half, more so on the left side of the epigastrium than on the right. Well marked epigastric pulsation. On the right movements are fairly good. "On palpation, below the umbilicus, the walls are not held firmly, and fairly deep palpation may be made without much resistance. No masses are palpable. There is a marked increase in resistance above the umbilicus and in the epigastrium. Here there is very distinct tenderness though it is not exquisite, and the walls are held quite firmly, the patient resisting voluntarily; there is no definite muscle spasm. On deep inspiration one can make out an indefinite mass in the epigastrium, the lower border of which is felt extending across the median line about midway between the umbilicus and the tip of the ensiform and reaching upwards to the left costal margin. This ridge feels somewhat irregular though it cannot be definitely determined. The percussion note over this mass is tympanitic; it lies apparently behind the stomach. No mass is felt in the right hypochondrium. The edge of the liver is not palpable."

The temperature was normal, ranging during the few hours that he was on the medical side, between 97.6° and 98.6°.

A blood count showed: red blood corpuscles, 5,140,000 to the cu. mm.; colorless corpuscles, 33,700 to the cu. mm.; hæmoglobin, 82%.

An approximate hasty differential count showed in one hundred cells: small mononuclears, 6; large mononuclears, 5; polymorphonuclears, 89; eosinophiles, none.

The *gastric contents*, after an Ewald test meal, amounted to 22 cc. of a fluid of a bright green color with flaky particles. The supernatant fluid is opalescent, the odor characteristic; total acidity, 33; hydrochloric acid, 19; no lactic acid. Microscopically: Bacilli of various kinds, no Oppler-Boas bacilli; many cells, for the most part leucocytes; few epithelial cells and yeasts.

Urine.—Yellowish brown; slightly turbid; 1022; strongly acid; no sugar; no albumin; urea 0.33 per cc.; no bile pigment; sediment: uric acid; two doubtful hyaline casts in centrifugalized specimen.

A diagnosis of acute pancreatitis was made and the patient was transferred to the surgical side, Dr. Finney performing an exploratory laparotomy on the same day. The peritoneal cavity contained no free fluid. The omentum seemed rather hard and indurated; no fat necrosis. The gall bladder was found to be rather thick but no stones were palpable. The tip of the omentum was adherent far down on the right side just below the gall bladder, and at this point there were two areas which looked like spots of fat necrosis. A number of similar points about one or two cm. in diameter were also found in the mesentery of the ascending colon. There was some general thickening of the pancreas which was most marked at the tail where there was a good sized mass. The spleen was large and surrounded by adhesions. The liver seemed small. The case was considered to be one of acute pancreatitis or possibly carcinoma of the tail of the pancreas and it was deemed inadvisable to explore further.

9 July, 1903. The patient's condition after operation was fairly good. In the evening the temperature was 104°, falling the next morning to 101.8°, the pulse improving correspondingly. To-day, however, the pulse has been weak, about 120, and strychnine and digitalin have been continued. In the afternoon the temperature rose to 102.3°. The patient began to wheeze, cough, and expectorate, and in the left side of the chest, both in front and behind, loud moist rales were heard; no tubular breathing.

11 December. The patient's condition grew steadily worse. There was frequent vomiting which was not relieved by washing the stomach. The pulse was weak and rapid. The abdomen was not distended. The temperature on the 10th ranged from 100.8° to 102.6°. On the afternoon of the 11th there were three profuse discharges of fresh bright blood from the bowels, death following soon afterwards, at 4 p. m.

Necropsy (No. 2135). Anatomical diagnosis.—Acute gangren-

ous pancreatitis with necrosis of the greater part of the pancreas; formation of fat necroses and perforation of stomach, duodenum and transverse colon; erosion of splenic artery with hæmorrhage into the pancreas and transverse colon; cholelithiasis; arterio-sclerosis of coronaries.

A partial necropsy was performed through the incision which was slightly enlarged. The *peritoneum* in the region of the incision showed a few ecchymotic areas. The great *omentum* was well developed and was slightly adherent to the hepatic flexure of the colon. The *cæcum*, *ascending* and *descending colon* were of a deep red color. . . . The *spleen* was adherent to the diaphragm and a mass could be felt in the region of the tail of the *pancreas*. On dissection between the *stomach* and *transverse colon* in the median line, a cavity was opened containing a dark red mass of semi-fluid blood clot mixed with a number of opaque, white, firm, friable masses. These masses possessed no definite structure but it was possible to see that at one time they probably had had an alveolar arrangement. There was a fæcal odor. The abdominal organs were removed entire and on cutting through the *œsophagus* a few small blood clots escaped. In tearing through the adhesions between the spleen and the diaphragm another cavity containing similar material was opened; this proved to be continuous with that which was first described. On careful examination of the transverse colon an opening was found in its superior surface 1.5 cm. in diameter with fairly smooth edges. This was situated about 5 cm. to the right of the middle line. The mucosa of the colon in this region was deeply blood-stained as well as the surrounding tissue in the cavity wall. The stomach was now opened along the greater curvature; a small quantity of slightly reddish fluid escaping with a few of the opaque white masses previously mentioned; the latter were most numerous near the pyloric orifice. About 9 cm. from the cardiac orifice on the greater curvature, and 3 cm. posterior to the attachment of the gastro-colic omentum on the posterior wall of the stomach, were two openings, both communicating with the cavity above mentioned. The larger and posterior was 9 cm. in diameter; the smaller, anterior, 2 mm. in diameter. The gastric mucosa excepting for these openings was normal and of the usual pale pink color with practically no evidence of blood staining. The edges of the ulceration as seen from within the stomach were smooth and fairly regular in outline. There was no evidence of thickening. The opening into the stomach was now continued into the duodenum along its right side. About 3 mm. below the pylorus on the left side of the duodenum, adjoining the pancreas was another large irregular opening, 1.5 cm. in diameter; the edges were smooth, the outline showing a few indentations. This communicated directly with the cavity previously mentioned. On continuing the opening into the duodenum a second opening was found just internal to the papilla of Vater, about 2 cm. in diameter. This resembled the first opening described in the duodenum in possessing smooth edges and an irregular outline and in communicating with the cavity above described.

The *gall bladder* was opened and found to contain nine small, angular, facetted, reddish-colored gall stones, the largest measuring 5 mm. in diameter. The *cystic duct* contained no gall stones and was patent. The *common bile duct* was patent and contained no stones. Its opening was situated just externally to and to the right of the second opening into the duodenum. The duct of Wirsung could not be found in the papilla, but on carefully passing a probe through the common duct, at the base of the perforation just internal to the papilla it could, by slightly altering its course, be passed through the papilla. The duct of Santorini could not be found.

On making a section through the head of the pancreas, a portion of normal pancreatic tissue corresponding to the head and measuring 1.5 cm. in transverse thickness and 3 cm. in antero-posterior diameter, could be distinctly seen. The left part of this normal tissue with the duodenum formed the right of the cavity which was bounded above by the stomach and passed outward between the stomach and the spleen, extending upwards to the left from a point about 4 cm. to the left of the middle line. Another arm passed below and behind the spleen and occupied the region of the tail and the left part of the body of the pancreas. The main cavity lay between the colon and stomach and occupied the position of the body and greater part of the head of the pancreas. The inferior boundary was formed by the folds of the slightly developed transverse meso-colon. The whole cavity contained the substance previously mentioned. There was a marked fæcal odor. No trace of normal pancreatic tissue was found with the exception of the small portion of the head previously mentioned. The source of the hæmorrhages was from the splenic artery as far as could be observed in the short time allowed for the examination.

Examination of the pancreas with the exception of the portion of the head previously described showed that it was replaced by masses of firm, whitish, friable, opaque material with a fæcal odor. Some semblance of the alveolar structure of the pancreas could be made out in places. This was mixed with recent blood clot, semi-fluid and apparently only a few hours old, suggesting that the hæmorrhage was a secondary and probably terminal event. The dissection of the head of the pancreas showed that the common bile duct and the duct of Wirsung united at least 1 cm. below the orifice of the papilla of Vater.

* * *

Since the renewal of interest in diseases of the pancreas which followed, especially, the notable work of Fitz[3] we have gained much knowledge concerning the nature, frequency, and symptoms of acute pancreatitis.

The experimental observations of Hildebrand,[4] Koerte,[5] Dettmer,[6] Hlava,[7] Williams,[8] Flexner,[9] and others, demonstrated that acute pancreatitis might be produced by various mechanical and chemical injuries to the organ.

The direct relation between the escape of pancreatic juice into the surrounding tissues and the development of disseminated fat necrosis, first suggested by Langerhans,[10] may be regarded as proven since the demonstration of a fat-splitting ferment in the necrotic foci by Flexner,[11] and the investigations of Opie.[12]

The notable observations of Halsted[13] and Opie[14] would seem to indicate that one of the most important causes of acute pancreatitis is the retrojection of bile into the pan-

[3] Boston M. & S. J., 1889, CXX, 181, 205, 229.

[4] Centralbl. f. Chir., 1895, XXII, 297.

[5] Berliner Klinik, 1896, No. 102.

[6] Inaug. Diss., Goettingen, 1895.

[7] Bulletin international de l'académie des sciences de Bohême, 1897.

[8] Boston M. & S. J., 1897, CXXXVI, 345.

[9] Johns Hopkins Hosp. Rep., Balto., 1900, IX, 743.

[10] Arch. f. path. Anat. (etc.), Berl. 1890, CXXII, 252, and Festschr. Rudolf Virchow, 80, Berlin, 1891.

[11] J. Exper. M., N. Y., 1897, II, 413.

[12] Contributions to the Science of Medicine, dedicated to William H. Welch, Johns Hopkins Hosp. Rep., 1900, IX, 859.

[13] Johns Hopkins Hosp. Bull., Balto., 1901, XII, 179.

[14] Johns Hopkins Hosp. Bull., Balto., 1901, XII, 182; also Am. J. Med. Sc., 1901, CXXI, 27.

creatic duct, such as may occur in connection with the passage of a stone or its lodgment in the diverticulum of Vater, in cases where the opening of the duct of Wirsung occurs at a point sufficiently far from the outlet of the common duct to admit of its patency at the time of obstruction of the latter. Repeated experiments have shown the possibility of producing pancreatitis in this manner. Apart from Opie's and Halsted's observations a study of the literature reveals the striking frequency of the sequence of acute pancreatitis upon cholelithiasis. In my first case of pancreatitis the onset of an acute hæmorrhagic inflammation followed immediately the passage of a stone which was found, at necropsy, in the common duct.[15]

Peiser[16] has recently called attention to a suggestive relation between acute pancreatitis and parturition. Eight out of 121 cases collected by him occurred during the puerperium. He accordingly suggests that the changes which give rise to this process may be similar to those occurring in the liver and other organs in eclampsia, and due possibly to like toxic substances. Münzer,[17] on the other hand, calls attention to the possibility that the primary necrosis may follow embolism of small vessels in the pancreas with giant cells from the placenta.

Those cases of acute pancreatitis which go on to suppuration, the "subacute" form of Robson and Moynihan, have especial interest in that they alone are amenable to surgical treatment. In most of these cases the onset is as acute as in the hæmorrhagic form, but the symptoms are, as a rule, less aggravated and the changes are not at first of sufficient extent and gravity to cause the death of the patient. Subsequently the necrosis and secondary infections result in the formation of more or less extensive abscesses with the characteristic contents, in which may lie larger or smaller portions of the sequestrated necrotic pancreas. In view of the satisfactory results of prompt surgical interference, the question of early diagnosis in these cases is extremely important. As has been said the symptoms are more or less characteristic. The onset, sometimes ushered in by an attack of biliary colic, is usually characterized by sudden, intense, abdominal pain, localized, as a rule, in the epigastrium but often more or less general and associated with obstinate vomiting and collapse. The fever is not, as a rule, excessive. In some instances the attack may be followed by or associated with jaundice. In the course of a few days the acute symptoms subside, but there remains epigastric tenderness with fever, possibly chills, sweating and evidence of deep abscess. Vomiting is often obstinate. Not infrequently a deep mass may be felt. This mass, as is strikingly emphasized by our cases, may extend on either side into regions considerably distant from the normal limits of the pancreas. It may occupy a situation such as to suggest a paracholecystitis (Case IV) or a paranephritic abscess (Case I). It may be confounded with the results of perforation of the stomach, intestine, or gall-bladder. The cases reported emphasize, especially, this variability in the position of the tumor mass; in two, the tumor extended to the right of the median line; in one, to the left; in two, it lay about in the median line. A deeply-seated inflammatory mass in the upper abdomen, when perforation of the stomach, intestine, or gall-bladder is improbable, should always suggest a suppurative pancreatitis, especially if the onset has followed shortly after attacks of biliary colic.

In cases of this nature careful study of the excreta may be of a certain help. The gross observation of fatty stools is not of very great clinical importance, although Ury and Alexander[18] assert that a discharge of large quantities of liquid fat after the passage of solid, formed fæces is almost diagnostic of extensive pancreatic affection. The determination of the relation of neutral fat in the stools to the fatty acids and soaps may be of assistance. In extensive pancreatic disease there is an interference with the normal fat splitting in the intestine—amounting, ordinarily, to from 70 to 80 per cent of the fat. Before passing judgment upon either of these questions it is, of course, important that the patient should be subjected to careful experimental feeding. According to Ury and Alexander there are three possibilities with regard to abnormalities in the fat content of the fæces in pancreatic disease:

(1) There may be an increased quantity of fat with a diminished fat splitting.

(2) There may be an increased quantity of fat with normal fat splitting.

(3) There may be a normal quantity of fat with diminished fat splitting.

Unfortunately, the careful feeding necessary for thoroughly satisfactory observations of this sort, is usually impossible in acute pancreatitis.

Interference with the digestion of fat is often associated with deficiency in the proteid digestion. The mere discovery of muscle fibres cannot, however, be regarded as an abnormality, and, apart from the quantity of meat taken, it may depend upon various other conditions disturbing the movements, secretion, and absorptive powers of the small intestine. Oser[19] lays some stress upon the importance of the evacuation of quantities of solid fæces which are unduly large relatively to the diet taken.

Glycosuria is rare and of little diagnostic importance. One would expect it to follow only most extensive pancreatic destruction; we know nothing of any selective influence of acute inflammatory processes in the islands of Langerhans.

A test which may prove of considerable importance, is that suggested by Opie who, in one case of acute hæmorrhagic pan-

[15] Boston M. & S. J., 1889, CXXI, 506.

[16] Deutsche Zeitschr. f. Chir. LXV, quoted by Münzer, Centralbl. f. d. Grenzgeb. d. Med. u. Chir., Jena, 1903, VI, 490, 529, 573, 619, 664.

[17] Münzer, Centralbl. f. d. Grenzgeb. d. Med. u. Chir., Jena, 1903, VI, 490, 529, 573, 619, 664.

[18] Deutsche med. Wchnschr., 1904, XXX, 1311, 1345.

[19] Die pathognostischen Symptome der Pancreaserkrankungen, Die deutsche Klinik, etc., Berlin, 1901, 151.

creatitis was able to demonstrate the probable presence of a fat-splitting ferment in the urine; Opie[20] pointed out that there was a reasonable possibility that in acute pancreatitis traces of lipase might be demonstrable.

The recent observations of Hewlett[21] upon this question are of considerable importance. This observer has determined that lipase appears in the urine after a variety of insults to the pancreas of dogs; it is found in greatest amount as a result of experimental acute hæmorrhagic pancreatitis. The procedure adopted by Hewlett for determining lipase in the urine is a modification of the Kastle-Loevenhart method depending upon the hydrolytic cleavage of ethyl butyrate in a solution containing lipase, into butyric acid and alcohol. The urine is then extracted with ether and the amount of butyric acid determined by titration. The following is the method in detail: "Five cubic centimeters of urine are placed in each of three flasks. The urine in the second flask is then boiled. To the urine in the third flask are added three drops of a one per cent solution of phenolphthalein and N/10 sodium hydrate solution is allowed to run in from a burette until a faint pink color appears. The amount of sodium hydrate solution used is read off and a like amount is added to the first and second flasks. To each of these two flasks, the first of unboiled urine, the second of boiled urine, is then added twenty-five hundredths cubic centimeter of ethyl butyrate and one-tenth cubic centimeter toluene, and they are placed in a thermostat at 39° C. for about twenty hours. The toluene is added in order to prevent the growth of bacteria. At the end of this time each flask is taken out and sufficient N/10 hydrochloric acid is added to more than neutralize the alkali previously added by five-tenths cubic centimeter. Each specimen is then shaken in a separating funnel with fifty cubic centimeters of redistilled ether, and the ether is separated. After adding three drops of a one per cent solution of phenolphthalein to twenty-five cubic centimeters of pure alcohol, the latter is brought to the neutral point. The ether extract from the separating funnel is now added to the neutralized alcohol and its acidity is determined by titrating with N/20 potassium hydrate solution. Any decided difference between the acidity of the ethereal extracts of the boiled and of the unboiled urine is due to the butyric acid formed by the cleavage of the ethyl butyrate; and where the difference in acidity is at all great the odor of this butyric acid can be easily recognized."

It is greatly to be regretted that this test was not made in the first case. Directions had been left to carry it out which were interfered with by an unfortunate accident.

It is an interesting fact that in three of these cases the presence of gall stones was proven. In two they were found at autopsy. In a third, our last case, the gall bladder was not explored but repeated attacks of characteristic biliary colic had occurred, one at the onset of the pancreatic symptoms. In the other two instances the gall bladder was not examined although in Case IV the history was decidedly suggestive of cholelithiasis.

Consideration of these cases also tends to impress one with the feeling that pancreatic disease ought to be more commonly recognized than is the case. The complex of symptoms is, in many instances, characteristic. In all of these cases a diagnosis was made. In the four cases which fell under our observation a positive diagnosis was made in two instances, and in one, pancreatitis was suggested as the strongest possibility. In Case IV the correct diagnosis was made by Professor Halsted. In Case III, which I did not see, Dr. Bloodgood recognized the condition.

The most important point brought out by the review of these cases seems to me to be the favorable result of early operation. Of the four instances of suppurative pancreatitis which were operated upon, three recovered. In Case II, in which there was a fatal result, the patient had been in a miserable condition for three weeks before operation.

The fourth instance was clearly a case of gangrenous pancreatitis.

Final considerations:

(1) A consideration of these five cases would seem, in the first place, to emphasize the importance of the relation between cholelithiasis and pancreatitis.

(2) It should further call attention to the importance of an early diagnosis. Relief can be expected only from early operation and drainage, and while it may be truly said that a positive diagnosis is often difficult, yet there are few conditions with which suppurative pancreatitis is likely to be confounded, in which exploration is not the proper and conservative course.

[20] Johns Hopkins Hosp. Bull., 1902, XIII, 117.

[21] J. Med. Research, Bost., 1904, XI, n. s. VI, 377.

DIAPHRAGMATIC GROOVES ON THE LIVER.

By Robert Orton Moody, M. D.

Instructor of Anatomy, University of California.

(*From the Hearst Anatomical Laboratory of the University of California.*)

Introduction.

Grooves on the convex surface of the liver have been more or less carefully observed and studied since the close of the 16th century. Early in the 17th century Fernel (1602) and, sixty years later, Glisson (1666) described them and offered explanations for their existence, designated by Cruveilhier (1874) as "*opinions singulières.*" In the middle of the next century, Morgagni (1761) described some grooves found on the liver at the autopsy of an old woman, and about one hun-

dred years later Cruveilhier (1856) first distinguished the two kinds of grooves now designated costal and diaphragmatic.

Costal grooves occur most frequently on the lateral surface of the right lobe, extending sometimes upon the anterior surface. According to some authors they are impressions caused during life by compression or constriction of the thorax or abdomen due to tight clothing or to chronic pulmonary lesions. They are single or multiple, broad and superficial, rarely narrow and deep, their direction corresponding to that of the ribs which made them. Soulé (1902) describes three varieties: (1) very faint impressions that disappear after the liver has been removed from the body for a certain time; (2) simple grooves deeper than impressions forming a definite, permanent groove covered by normal peritoneum; (3) cicatricial grooves which may be shallow or deep, temporary or permanent. The distinguishing characteristic is the replacement of the peritoneum lining the grooves by cicatricial tissue, which is permanent even though all other signs of the groove disappear.

In bodies autopsied soon after death these grooves, according to Leue, are found most frequently in women. A systematic examination of 516 bodies autopsied at Kiel showed such grooves to be present in 56 per cent of the females and in only 5 per cent of the males. In this laboratory where most of the subjects are male, costal grooves, usually multiple, have been found in a large percentage of the cases. Since dissecting material is not available for embalming until 48 or more hours after death, these grooves may be due to post-mortem pressure of the liver against the ribs with the body supine.

Diaphragmatic grooves, single or multiple, occur most often on the ventral and superior surfaces of the right lobe of the liver and on the ventro-lateral border. They may also exist on the lateral or dorsal aspects of this lobe and rarely on the ventral surface of the left lobe. In a large percentage of cases they are approximately parallel with the falciform ligament and with one another and so far as observed here are always at an angle with the direction of the ribs. In form they vary from mere slits to furrows 7 millimeters wide at the bottom, in length from 1.5 to 11 centimeters and in depth from impressions of less than 1 to sulci of 18 millimeters. Their sides may be parallel or widely diverging, rarely slightly converging. They may or may not contain folds of the diaphragm.

Besides these grooves which have no apparent phylogenetic or ontogenetic significance, Thomson (1899), Rathcke (1896) and others have described and figured narrow fissures commonly present on the Spigelian and quadrate lobes and on the inferior surface of the right lobe. These are held to be persistent embryonic characters, corresponding to fissures more or less distinct in the adult anthropoids and lower forms.

Since Cruveilhier's (1856) recognition of two classes of grooves, the diaphragmatic have been studied by French, German, and Italian investigators who have offered various theories to account for their occurrence. Turner (1898) in England has paid some attention to these grooves but no contributions to the subject have been published by American anatomists. Except brief references in Quain's Anatomy (1898) and in some text-books on pathology, there is no literature on this subject in the English language. It is therefore intended to give a brief résumé of work already recorded, together with results obtained in this laboratory.

HISTORY.

That these grooves are of common occurrence, that they exist most frequently on the convex surface of the right lobe of the liver, that they are usually multiple and nearly parallel with the falciform ligament, seems to be the consensus of opinion. But in regard to the sex in which they are most often found, to their presence in youth and infancy, to their association with certain pathological conditions, to their relations with the diaphragm and to their cause, widely differing opinions are expressed.

Concerning the frequency of these grooves there is great scarcity of adequate information, Mattei (1890) alone having kept a record of the total number of bodies examined. He found sixty-nine grooved livers out of one hundred and forty-six cases, about 41 per cent. Other authors have recorded only the sex of the individual and the total number of grooved livers found.

The sex in which these grooves most commonly occur has been the subject of much discussion. Turner (1898), Zahn (1882), and Jacquemet (1896) claim they are found more frequently in men; Charpy (1901) asserts them to be rare in men but common in women. The fifty-eight cases reported by Séglas were all female. The autopsies, however, were made at the Salpêtrière, a home for aged women. Cruveilhier (1874), who also noticed the grooves in a large number of bodies at the same institution, does not express an opinion as to their frequency in men. Buy (1904), who found these grooves in twenty-nine women and twenty men, also claims that they occur much more commonly in women, but he takes no account of the sex or number of bodies in which grooves were not found. In a systematic examination of 146 cadavers, 87 male, 59 female, Mattei (1890) found grooved livers in 26 men and 35 women.

Excluding Séglas' (1902) fifty-eight cases which can have no bearing on relative frequency in the two sexes, the following table gives the number and sex of all cases of which record has been found:

TABLE I.

	Male.	Female.	Unknown.
Mattei	26	35	0
Buy	20	29	3
Kerr[1]	14	1	3
Jacquemet	7	1	0
Tigri	3	0	0
Guéniot	0	2	0
Caryophyllis	1	0	0
Michaut	1	0	0
Jackson[2]	1	0	0
Bagaloglu	0	1	0
Meckel	0	0	1
	73	69	7

The age at which these grooves may appear is another disputed point. Jacquemet (1896) claims that they are found only in subjects over fifty years of age, at the same time recording a case of forty-eight years. Charpy (1901) says they do not exist before the fifteenth year and are most frequent in old age. Buy agrees with him and lays special stress on the fact that they are never found in infants. On the contrary, Mattei (1890) believes that they may be found at all ages and even during intra-uterine life, but gives no account of finding them in the youth, infant or fœtus. Orth (1888), however, reports the occurrence of most beautiful sagittal furrows on the liver of a child which, born prematurely at seven months, died soon after birth.

Data upon the location of these grooves are more satisfactory. Buy (1904) finds them most often on the highest part of the superior surface of the right lobe sometimes extending upon the dorsal surface, but never reaching to the ventro-inferior border, although they occasionally reach to the center of the diaphragm, or even to the right wall of the vena cava. He also finds them on the left lobe, usually fine and faintly marked. In one case, however, the groove on the left lobe was more distinct than those on the right. Meckel (1812) reports a similar condition, where there were six well-marked grooves on the left lobe and three on the right; while Mattei (1890) finds them sixty-six times on the right lobe and four times on the left.

The record of the number of grooves is also complete and shows them to be usually multiple. They are said to vary from 1 to 9, Jacquemet (1896) claiming that their occurrence singly is rare, while Soulé (1902) makes their multiplicity an important distinction between them and costal grooves. Buy (1904) observes them occurring most frequently in twos and threes.

The direction of these grooves is described as "antero-posterior," "extending from the thick to the thin border of the liver," "lying in the long axis of the body," "longitudinal" and "parallel with the falciform ligament." According to Buy (1904), their direction is antero-posterior, they are parallel in the middle, converging dorsally and diverging ventrally. Rarely the converse is true. They are often curvilinear, the concavities looking toward the falciform ligament when placed laterally, away from it when placed near the ligament, or occasionally toward each other thus ( ). In one case he found a groove shaped like an italic letter *S* and in another one like the letter Y.

The form as given by different authors is deep and narrow or shallow and broad, with varying proportions. The length is said by Buy (1904) to be usually from 5 to 6 centimeters, with a minimum of 2 and a maximum of 9. He also says they habitually increase in length toward the median line. Jacquemet's (1896) limits are from 3 to 10 centimeters, the grooves increasing in length from right to left or from left to right. Caryophyllis (1889) found four grooves ranging in length from 10 to 12 centimeters; thus an extreme variation from 2 to 12 centimeters is reported. Most writers describe the grooves as narrow, but Buy (1904) claims that their breadth is relative to their form and indicates two classes, the one gutter-like with a width of from 5 to 12 millimeters, the other, which he designates as true grooves, are narrow, only a few millimeters in breadth. There is also much variation in depth. Mattei (1890) finds some sulci so shallow as to be seen only on the most careful inspection, others 15 millimeters deep. Jacquemet's (1896) series ranges from 2 to 11 millimeters and Michaut (1888) records a case of 25 millimeters, while Buy (1904) gives as his limits less than 1 centimeter to 2.3 centimeters. He holds that the grooves may increase in depth from the median line laterad or the reverse or the deepest grooves may lie in the middle of the series, flanked by shallower grooves, the first arrangement being the most frequent. Moreover the deepest is usually the longest and the depth increases with the age of the subject, a fact also noted by Mattei (1890).

Much stress is laid on the condition of the diaphragm and its relation to these grooves. Observations and opinions on the former may be placed in one of two general classes: first, the diaphragm overlying a grooved liver always has folds or hypertrophied digitations or fascicles of the musculature; to this the majority of authors agree. Second, that such a folding or hypertrophy may or may not exist, a view held by only three authors, Buy (1904), Guéniot (1898), and Bagaloglu (1899).

Charpy (1901), Caryophyllis (1889), Cruveilhier (1874), and Tigri (1873), believing folds or digitations to be always present, record no observations as to other conditions of the diaphragm. Zahn (1882) agreeing with these authors claims that the hypertrophied digitations of the diaphragm have their origin at its costal insertions and may degenerate, leaving only the two serous layers and some connective tissue. Séglas (1886) finds the diaphragm sometimes adherent to the liver and observes stripes of degenerated muscle fibers in the diaphragmatic musculature so placed as to have no definite relation to the grooves in the liver. An entirely different condition is described by Mattei (1890), who believes that

[1] Recorded in this paper.

[2] Not published but record given to me by Dr. Jackson, of University of Missouri.

there is a congenital unequal distribution of the musculature of the diaphragm, resulting in thickened muscle bundles alternating with thinned areas.

Of the second group Buy (1904) alone discusses in detail the condition of the diaphragm. He finds three possibilities: first, it is unmodified and passes over the grooves like a bridge; second, still bridging the grooves, it is uniformly thickened; third, it sinks more or less deeply into the grooves, is thin and transparent over the intermediate mounds of liver and is thickened at the bottom of the grooves. This he believes due to functional hypertrophy and a sliding downward of the muscle fibers from the sides, so that sometimes there is no muscular tissue at the neck of the groove. The mounds of liver between the sulci cause a stretching and consequent thinning of the overlying musculature.

Connected very closely with the condition of the diaphragm is its relation to the grooves. Charpy (1901) states that an examination of the liver and diaphragm in situ shows that the folds exactly fill the grooves and with this Tigri (1873), Mattei (1890), and Séglas (1886) agree. On the contrary Buy (1904) finds, as already mentioned, that the diaphragm may bridge the grooves or may fill them completely or in part. Agreeing in the main with Charpy (1901), Zahn (1882) admits that sometimes the fold only partly fills the groove, when the depth is great.

Another point of interest is the condition of the peritoneum and parenchyma at the bottom of the grooves. That both are normal is held by Charpy (1901), Orth (1888), Séglas (1886), Jacquemet (1896), and Guéniot (1898). Buy (1904) and Mattei (1890) agree that the peritoneum is unaltered but do not mention the parenchyma. The former adds that peritoneal adhesions never occur at the bottom but on the sides of the grooves or on the projecting liver surface. As opposed to this Liebermeister (1864) and Klebs (1868) find alterations in both, the peritoneum having become thickened and the parenchyma having degenerated and atrophied.

The pathological conditions associated with these grooves according to some authors are many, while others have made no record of their co-existence. Charpy (1901) states that the liver is bomb-shaped, its vertical diameter is increased, and the inferior edge, extending beyond the costal margin, approaches the iliac crest. The gall bladder is pinched laterally and projects downward, the Spigelian lobe becoming pediculated, thin and elongated. The inferior part of the right lobe becomes separated, forming the lobe of Riedel. Some portions of the left lobe atrophy and are transformed into membranous appendices which fold in every direction. There are also found on the same subjects external malformations of the thorax and in the abdomen, bilocular stomach and movable kidney. In general Buy (1904) agrees with these observations but emphasizes the constant co-existence of signs of habitual compression of the thorax, the liver and other abdominal viscera. He enumerates as these signs, deformed costal skeleton, contraction of the transverse diameter of the chest, decreasing of the xiphoid angle, changes in the liver described by Charpy (1901), which, together with costal grooves, characterize the "liver of constriction," costal grooves on the spleen, enteroptosis and nephroptosis. A different group of co-existent pathological conditions is given by Liebermeister (1864), whose observations were confirmed by Zahn (1882), Klebs (1868), Jacquemet (1896), and Séglas (1886). These authors found in most cases that the grooves were associated with diseases of the lungs and pleura, resulting in difficult respiration; double goitre compressing the trachea was also noted by Zahn (1882). Séglas (1896) examined the records of autopsies held at La Salpêtrière for a period of five years and found fifty-eight cases of grooved livers, in only five of which the lungs were sound. In the remaining fifty-three cases, pleurisy was present in twenty-four, hydrothorax one, pulmonary congestion twenty-four, pneumonia twenty-two, broncho-pneumonia eight, chronic bronchitis four, emphysema three, tuberculosis two. These lesions were combined in a different manner in thirty-six cases. In six of the remaining seventeen, both lungs were involved; one had hydrothorax; two, pulmonary congestion; three, broncho-pneumonia. On the right side alone acute and chronic pneumonia were present in four cases and broncho-pneumonia in one. On the left side alone, pneumonia was found four times, pulmonary congestion once, pleurisy with thickening and adhesions once. The pathological conditions found by Tigri (1873) and Mattei (1890) concern the diaphragm and have been enumerated in the consideration of that structure.

CAUSES.

The desire to account for these grooves has led to much discussion and to the development of several distinct theories which may be placed in one of three classes. The oldest hypothesis, that of constriction by clothing, is suggested by Morgagni (1761), who, in reporting his one case, an old woman, remarks that if such grooves were found only in women, there might be some ground to suspect a causal relation in the pressure exerted by the corset. This view is more positively stated by Cruveilhier (1874) who, finding these sulci in a large number of old women at the Salpêtrière, concludes that constriction by the corset causes folds in the diaphragm, these in turn creasing the liver. Charpy, a strong advocate of this "constriction" theory, has in a letter to me extended its application to grooved livers in men, claiming that tightly drawn belts would force the livers upward into the narrower part of the diaphragmatic dome thus subjecting them to increased lateral pressure. After a careful study of this problem in Charpy's laboratory, Buy (1904) accepts the constriction theory and vigorously defends it, giving the following reasons: the much greater frequency of grooves in women; the constant co-existence of signs of habitual external thoracic compression; the presence of these grooves on the constriction type of liver; concomitant deformities of abdominal viscera; complete absence of such grooves in infants and increased frequency with advancing years. He

asserts that they are due neither to a congenital condition nor to a teratological disposition of the diaphragm, nor to its irregular contraction dependent upon difficult respiration. Two types of the grooved "constriction livers" are recognized, masculine and feminine, the former caused by "low constriction" as of a belt, the latter by "high constriction" as of a corset. The superior surface of the masculine type is characterized by the presence of a marked bomb, bearing one or more grooves of varying depth. This form he attributes to the crowding of the liver upward when the dimensions of the abdominal cavity are decreased, thus causing a heaping and consequent folding of the liver substance sometimes accompanied by, or resulting in, a corresponding fold of the diaphragm. Two varieties of the feminine type are described; the one liver is flat and relatively slightly deformed, often anteverted, marked by shallow, oblique, diverging grooves situated only on the cephalic surface; the level of greatest pressure in these cases is high. The other liver, compressed transversely, much deformed, is the type of "constriction liver," costal impressions are distinct, the right lobe is high, thick, bomb-shaped, grooved longitudinally, elongated, often crossed near its caudal border by a transverse groove, separating what is known as a "lobe of constriction." The pressure in this type is at a lower level than in the preceding, but in both cases the lower part of the thorax is narrowed, resulting in a consequent folding and grooving of the plastic liver. The masculine and feminine types are not, however, restricted to the male and female sexes respectively; the former frequently occurs in women and the latter occasionally in men. Bagaloglu (1899) accepts the constriction theory, as does Guéniot (1898) for those cases in which there are no corresponding diaphragmatic folds.

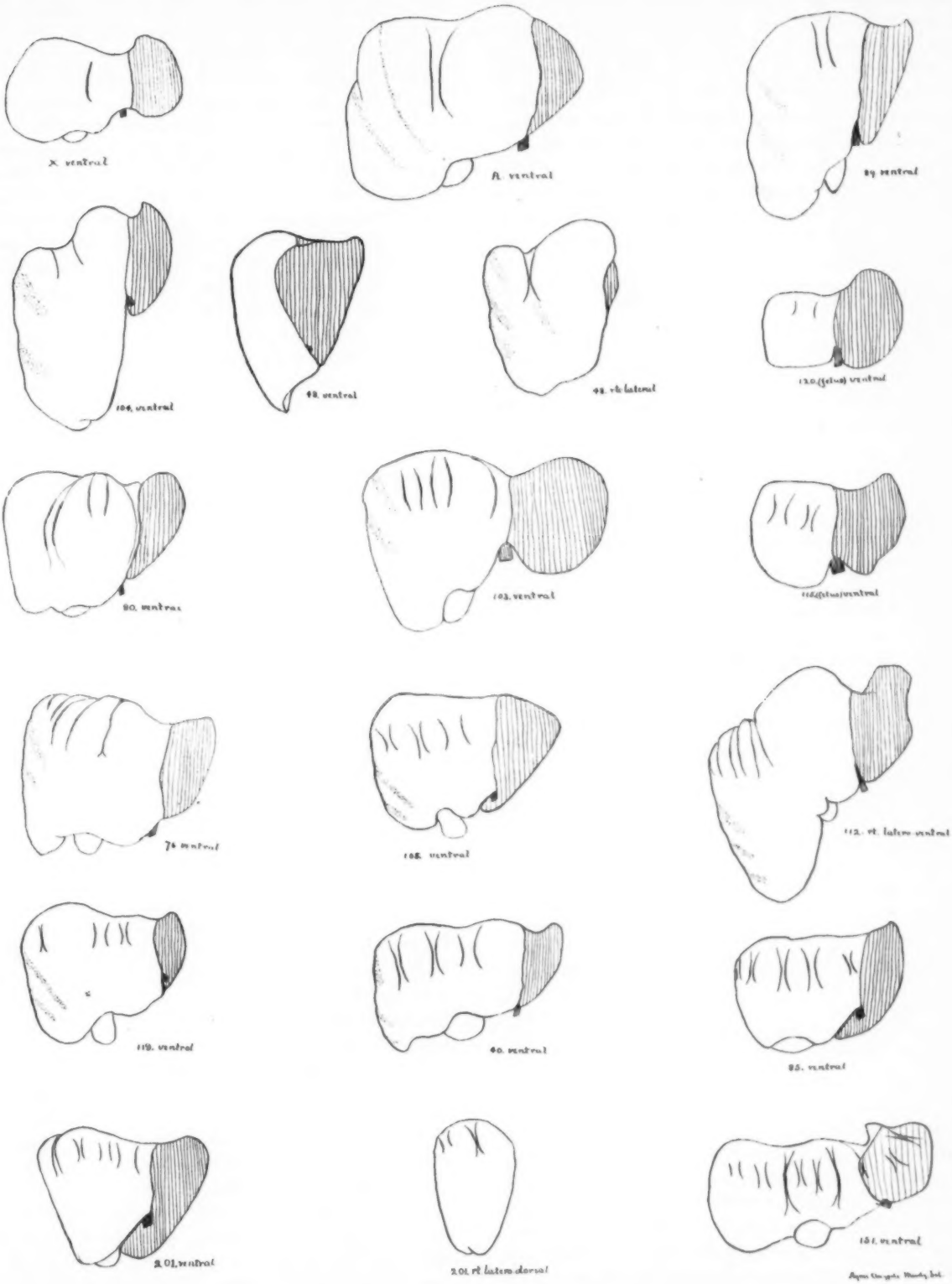
Broadly speaking the next hypothesis also involves constriction, but with this difference, that the pressure is due, not to external artificial causes but to internal pathological conditions. Dyspnea, resulting from difficult expiration, is held by Liebermeister to be the fundamental cause of these sulci, which he calls expiratory grooves. He asserts they are never formed by the diaphragm but are due to the pressure of the caudal borders of the ribs, which are drawn in by the exaggerated action of the external oblique and transverse abdominal muscle during forced expiration. This muscular action is often reinforced by the permanent depression of the diaphragm commonly accompanying difficult expiration, and limiting the upward movement of the liver. This action must be long continued to produce permanent grooves. To this interpretation Klebs (1868) agrees, but believes that scoliosis, rachitis, and pressure of corsets may also narrow the thorax transversely and thus cause such grooves. Zahn (1882) says he is in accord with Liebermeister (1864) in the belief that the grooves result from long continued difficult respiration but differs fundamentally as to the mechanism of the process. The primary cause is impeded *inspiration*, to compensate for which a gradual hypertrophy of certain portions of the diaphragm takes place. This thickening begins at its costal insertions and gradually extends centrally, so that even before grooves have appeared on the liver, such a diaphragm viewed by transmitted light shows the existence of thickened fascicles separated by thinner areas. Ultimately these thickened digitations by downward pressure during the contraction of the diaphragm cause grooves on the liver. This author is not convinced that the corset can primarily form sulci but it may increase the depth of those already existing. Séglas (1886), Michaut (1888), and Jacquemet (1896) all accept this view with slight modifications.

The two remaining theories are held by those who believe the primary cause to be a congenital condition of the diaphragm. Mattei (1890) claims that there exist in the diaphragm even before birth alternate thin and thick areas, the musculature sometimes being entirely absent in the thin parts; that since the growth of the liver is greatest along the lines of least resistance, the parenchyma pushes up beneath the thin areas with the result that grooves and elevations alternate on the surface of the organ. He denies the action of any other cause, admitting only that grooves may be deepened by the physiological contraction of the thickened muscle bands lying in them. The other theory advanced by Tigri (1873) differs fundamentally from the preceding. He maintains that the sulci are due to the presence of teratological, cylindrical, muscular reliefs on the caudal surface of the diaphragm, which by constant close contact impress the liver surface with corresponding grooves. He associates these reliefs with other abnormal muscular conditions of the diaphragm. He also denies the action of any other cause. Orth (1888) must likewise be classed with those who believe that the grooves may be congenital, basing his belief on the fact that the capsule and parenchyma at the bottom of the grooves remain unaltered; at the same time he is unwilling to deny the claims of Zahn (1862) and Liebermeister (1864).

Material.

To the foregoing history it is now possible to add the record of 17 cases found in this laboratory and 16 from the museum of Cornell University kindly loaned by Dr. Kerr. Of the 17 cases, 5 were from adult and 2 from fœtal subjects. In accordance with the law, bodies cannot be delivered to this department until at least 48 hours after death. Thus in all subjects received here post-mortem changes have taken place before embalming. The preserving fluid used in 11 of the adults was the carbolic mixture[1] advocated by Mall (1896), in 2 an arsenic-formalin combination; the history of the remaining 2 is wanting. After the injection of 6 quarts of the carbolic mixture under constant pressure, some of the bodies were placed in tanks over wood alcohol and in a few months were transferred to vats containing 3 per cent of carbolic acid; others were put directly into the vats. With the exception of subject 201, which lay on the right side, all subjects are embalmed in the supine position and in

[1] Carbolic acid one part, alcohol two parts, glycerine two parts.


X. ventral
A. ventral
89. ventral
104. ventral
92. ventral
93. rt. lateral
120. (fetus) ventral
80. ventral
103. ventral
116. (fetus) ventral
74. ventral
108. ventral
112. rt. lateral ventral
119. ventral
90. ventral
85. ventral
201. ventral
201. rt. lateral dorsal
151. ventral

the tanks have that position best suited to advantageous use of the space. Of the adult subjects received here about 79 per cent are old males, 7 per cent old females, 13 per cent young males, 1 per cent young females. The fœtal material is preserved either in alcohol or formalin; the 2 subjects in which grooved livers were found, were in alcohol.

The great variety of size and form found among these livers as shown on page 369 made it convenient to group them for description according to the number of grooves present; also for convenience the sulci are numbered from right to left.

Livers with One Groove.

Of these there were six, five adult, one fœtal; three male, one female, two unknown. They differ widely as to form, weight, size, and character of the sulcus. Of the entire series X approaches most nearly to the form and size of the His model, the differences between them being no greater than may exist between any two normal livers. It is not bomb-shaped nor deformed in any other way, its only peculiarity being a moderately deep, curved, slit-like furrow on its ventral surface.

In extreme contrast to this is A, which shows a condition usually considered uncommon but present to some degree in 9 of these cases; this liver lying almost wholly in the right hypochondrium, has an unusually broad lateral surface and the so-called dorsal surface looks mesad. The organ is much enlarged and the right lobe elongated; it is marked by two faint costal impressions and on the lateral surface by a long, wide, moderately deep, diaphragmatic sulcus extending vertically. A marked bomb projects upward and forward, bounded laterally by the sulcus.

Subject 89, a liver of moderate size having the right lobe much elongated, the Spigelian lobe and gall-bladder both pinched and elongated, also lies mainly in the right hypochondrium. It is so flattened that the dorsal and inferior surfaces lie in one plane, which looks mesad. There are three costal impressions and on the lateral surface one faint sulcus which is broad and very shallow. There is a strong resemblance between 89 and 104, the next to be described. This too is narrowed transversely and lies chiefly in the right hypochondrium, its much elongated right lobe extending into the right lateral abdominal region; the gall bladder is elongated but the Spigelian lobe is normal in form. The dorsal and inferior surfaces lie in the same plane and look mesad. A well-marked bomb projects from the ventro-lateral border, just laterad of which is a wide, rather deep groove; two costal impressions lie dorsad of the groove.

Of moderate size, not elongated, situated entirely in the right hypochondrium, except for the small flattened extremity of the left lobe, 48 is peculiar on account of a distinctly fœtal position of the gall bladder, which lies in a fossa terminating three centimeters from the inferior border of the right lobe. As in the three preceding livers the dorsal and inferior surfaces lie in the same plane and look mesad. A distinct bomb is seen on the ventro-lateral border. On the lateral surface close to the dorsal border, extending upon the superior surface and containing a fold of the diaphragm is a long, deep sulcus, very narrow at the bottom, spreading at the top; costal impressions groove the dorsal border. In this subject, a male of 43 years, the diaphragm is firmly adherent to the liver between the leaves of the coronary ligament and to the chest wall as high as the fifth interspace, a little laterad of the nipple line and as high as the ninth rib in the mid-axillary line; it is also firmly adherent to the base of the right lung. On the superior surface there is no indication of the fold running nearly parallel with the 8th rib so distinctly seen on the ventral surface. The pleural surfaces of the fold are firmly bound together by adhesions which are continuous with a thickened mass of scar tissue covering a large area in its vicinity. Both the musculature in the fold and the underlying peritoneum are distinctly thickened. The lungs are tubercular, the right being firmly adherent to the chest wall and to the diaphragm over a large area surrounding the fold. Another abnormality in this subject was a bilocular stomach. The last of this group, 120, is the liver of an eight months' female fœtus; it appears normal in every way except for a faint, broad, shallow sulcus on the ventral surface near the lateral border.

Livers with Two Grooves.

Of the livers with two grooves 80 is moderate in size, lies chiefly in the right hypochondrium, has a prominent bomb projecting from the ventral and lateral surfaces. This is bounded laterally by a long, wide diaphragmatic groove of considerable depth, reaching from the superior surface to near the inferior margin, and carries on its summit a faint, shallow sulcus. The lungs in this subject, a male 78 years of age, were normal with slight lateral pleuritic adhesions. The inferior surface in this liver is distinct from the dorsal which looks nearly mesad.

From an adult female subject, 103, the liver is of moderate size, somewhat elongated transversely, has two costal impressions and a small bomb directed ventrad. The dorsal and inferior surfaces are in one plane and look dorsad. Of the two diaphragmatic grooves the deeper, shorter and broader, lies on the ventral surface of the right lobe; the other very faint, is on the ventro-lateral border. The lungs showed no indications of disease; the right lung, however, had five lobes and was slightly adherent to the diaphragm.

The next specimen, 115, is most interesting because it is distinctly grooved and occurred in a male fœtus of about 9 months. The liver is in other respects approximately normal except for some post-mortem depressions and curling of the edges. The broader of the two grooves, 1.9 centimeters long, .15 centimeters deep, with widely diverging sides, is placed on the ventro-lateral border and is parallel to the falciform ligament and to the overlying muscular fibers of the diaphragm. The other groove situated a little mesad of the first on the ventral surface is 1.7 centimeters long, shallow, wide and directed obliquely so that the superior extremities

of the two grooves if continued would meet within a short distance. The muscular fibers of the diaphragm lying in this groove are parallel with it. There are no indications of thickened bands or thinned areas in the diaphragm, but a part of its tendon lies in the cephalic end of the longer groove (Fig. 3).

Livers with Three Grooves.

Liver 76 is flattened so that the inferior and dorsal surfaces are in one plane which looks dorso-mesad. It has two faint costal impressions and near the ventro-lateral border a small bomb. The sulci vary widely as to size and form; number one lying on the lateral surface near the dorsal border is short, wide and very shallow. Two, about a centimeter mesad of one, is 8 centimeters long, .5 centimeters wide at the bottom and 1.4 centimeters deep with widely divergent sides. The third, on the summit of the bomb, is 8 centimeters long, 1.8 centimeters deep and very narrow, its almost perpendicular sides making a sharp contrast with those of the other grooves. The great omentum, tucked up between the liver and the diaphragm and adhering to both, filled the two wide grooves and covered the narrow one without dipping into it, excluding the diaphragm from any close relation with the furrows. The pleura of both lungs was more or less adherent to the chest wall but not to the diaphragm (Fig. 4).

Like the preceding, this liver, 105, has its dorsal and inferior surfaces in one plane that looks dorso-mesad. It lies chiefly in the right hypochondrium and has two very faint costal impressions; there is no general enlargement nor projection into a bomb. The first groove situated on the dorsal border is very faint. The second, the most distinct, lies near it on the lateral surface; the third, very broad and shallow, is ventral. They are all parallel with the overlying fibers of the diaphragm which fits into them but has no permanent folds. In the neighborhood of the sulci there were on the diaphragm three thin areas alternating with two bands equal in thickness to the rest of the musculature but appearing thicker. The thorax had been cut in the median line, rendering it impossible to determine whether the thinned areas correspond with the grooves or with the ridges between them.

Enlarged in all its dimensions, 112 has a right lobe extending 3.5 centimeters below the costal border, a slight bomb on the ventro-lateral margin, and the peculiar flattened superior surface mentioned by Liebermeister which forms a right angle with the ventral surface. The Spigelian and quadrate lobes and the gall bladder are not, as customary, parallel with the falciform ligament but lie at an angle of 45 degrees to it. The dorsal and inferior surfaces are in one plane directed dorsad. The extremity of the left lobe is much flattened and elongated so that it overlaps the spleen and is in contact with the left parietes. A very shallow sulcus situated near the dorso-lateral border extends over the superior upon the dorsal surface. Two centimeters mesad is a second, passing over the same surfaces and curving so as to meet the preceding groove on the dorsal surface; its lateral portion is deep with widely diverging walls, its superior shallow, its dorsal slightly deeper. The third sulcus, 1.8 centimeters deep, .7 centimeters wide, parallels the second on the lateral and superior surfaces and has nearly vertical walls. All the sulci lie laterad of the bomb and are depressions below the normal surface of the liver; they are not longitudinal but oblique, their inferior extremities making an acute angle with the long axis of the body. Grooves two and three lodge diaphragmatic folds which exactly fill them. The adjacent pleural surfaces of these folds are firmly united by old adhesions, giving the cylindrical reliefs described by Tigri (1873). A thick layer of organized scar-tissue formed by pleuritic adhesions concealed any sign of the groove on the superior surface. The fold lying in groove three passes obliquely from the 8th to the 11th costal interspaces; number 2 passes from the inferior border of the 9th rib over the 12th, its fibers continuing into the right crus. Owing to the adhesions on the right side between the pleura of the thoracic wall and the diaphragm, the line of insertion of the latter was permanently changed to a higher level, corresponding very closely laterally and ventrally to the outline of the lung in expiration. These folds hardened in situ proved on microscopic examination to be the simple infoldings of the diaphragm and its pleura with a thick overlying mass of scar-tissue. The musculature of the folds was thickened. Tubercular nodules were present in both lungs and the pleura was extensively adherent to the thoracic parietes and diaphragm, especially on the right side and in the region of the folds (Fig. 5).

Livers with Four Grooves.

The first of this group, 119, from a male aged 76, is normal in size and shape except that the inferior and dorsal surfaces lie in one plane looking dorsad. The grooves present two distinct types, the deep slit and the shallow groove, the one with parallel and the other with widely diverging walls. These appear on surfaces which do not rise above the normal level, that is, the sulci are depressions of the liver substance. Groove one, a mere slit 1.5 centimeters long, lies on the lateral near the superior surface; the second of the same length but broader is on the ventro-lateral border, the other two shallow with widely diverging walls are on the ventral surface.

The next, 40, from a male subject 43 years old, is large, the right lobe not elongated, the left extending to the edge of the spleen. There is a bomb of large lateral but slight ventral projection; the grooves, 2 on the lateral and 2 on the ventral surface, are shallow, parallel, slightly converging superiorly, with widely diverging walls. The diaphragm is somewhat adherent to the liver over the right lobe, but has no indication of folds.

Livers with Five Grooves.

A moderate ventral bomb, a somewhat elongated gall bladder, the dorsal and inferior surfaces forming one plane and the presence of grooves, distinguish liver 85 from the normal. Sulci 4 and 5 lie on the bomb, 3 bounds it laterally, 1 and 2

are on the lateral surface, 3 and 4 converge toward the superior surface and are long and deep with steeply sloping sides.

Although the next subject, 201, a male aged 80, was embalmed lying on the right side, the liver is not noticeably different from some of the preceding. The left lobe is elongated, nearly equal to the right in length and is flattened dorso-ventrally. The right, not elongated, with distinct dorsal and inferior surfaces, has 2 costal impressions and a slight lateral bomb on the summit of which is a short groove slit-like at the bottom, wide at the top, containing a permanent fold of the diaphragm which crosses obliquely the 8th and 9th ribs. The other grooves, one dorsal and three ventral, are wide and shallow without permanent folds. Except for slight adhesions of the left lung to a portion of the thoracic wall and to the diaphragm, there are no indications of diseased lungs or pleura. The diaphragm hardened in situ shows on microscopic examination that the fold consists of a thickening of the musculature only, the pleura passing smoothly over the fold. There is no thickening of the diaphragm overlying the shallow grooves, the directions of which correspond to that of the muscular fibers.

Liver with Nine Grooves.

The last adult case, 151, a female 78 years old, presents a number of interesting conditions. The liver which resembles the fœtal type in the nearly equal size of the right and left lobes and in its position in the epigastric and both hypochondriac regions, is unusually short and broad and so flattened that the dorsal and inferior surfaces lie in one plane directed dorsad. It is marked by 9 diaphragmatic grooves, 6 on the right and 3 on the left lobe. The only other liver with 9 sulci, reported by Meckel (1812) had this arrangement reversed. Groove 1, shallow, short and broad, is about 2 centimeters from the right lateral border. Two, similar in size and shape, is about 4 centimeters from the border. Three, a little further mesad, is long, deep, concave toward the falciform ligament, with parallel walls which slope from the opening of the groove dorsad and slightly mesad. This forms the lateral boundary of an oval mass of liver substance 9 centimeters long, 7 centimeters wide, which projects slightly beyond the adjacent surface and bears on its summit two well-defined sulci. The other boundary is groove 6, long, narrow, and concave laterad; its walls are not parallel, the one next to the mass is directed dorso-dextrad and the other is almost parallel with the ventral surface of the liver. The planes of grooves 3 and 6, if prolonged would intersect within a short distance. The left lobe has a large, flat, superior surface separated from the ventral by a distinct angle and a well-marked splenic impression on its dorsal surface. The remaining three grooves are on this lobe. Seven, close to and parallel with the falciform ligament, moderately broad and shallow, is for the greater part of its length on the ventral surface but extends upon the superior, where it curves, sinistrad. Groove 8 lying entirely on the ventral surface about 5 centimeters from 7 is very shallow and is directed obliquely toward the median line. The last of these sulci, about 2.5 centimeters from the left lateral border, parallel to it and the preceding groove, is the most distinct on this lobe and lies on both the superior and ventral surfaces.

The gall bladder contains an oval stone, the axes of which are respectively 4.7 and 3.7 centimeters in length. That part of the ventral surface of the gall bladder extending beyond the inferior border of the liver is firmly adherent to the diaphragm over an area measuring 2.5 x 3.5 centimeters.

In situ the diaphragm shows distinct folds corresponding to grooves 3, 6, 8, and 9, which disappear on its removal from the body. The crests and sides of the folds lying in 3, 6, and 9 are formed by thickened bands of musculature not flanked on either side by thinned areas, thus indicating that the thickening is possibly due in part to hypertrophy, not alone to sliding of the muscle fibers. In the region of 9, the diaphragm is thickened over an area greater than that indicated by the groove. The fold itself is also longer and deeper than the underlying sulcus, which points to the formation of the fold prior to the groove. The folds corresponding to grooves 3 and 6 converge superiorly and terminate independently at the tendon on either side of the vena cava. Superiorly they also converge and unite in the thickened area of adhesion between the gall bladder and the diaphragm. Notwithstanding this unusual convergence at the periphery, the folds are parallel with the musculature. The changed direction of the muscle fibers is due primarily to a cholecystitis resulting in an adhesion of the gall bladder to the diaphragm and subsequent formation of scar-tissue, which by thickening and contraction tends to draw together fibers within the area of its influence. This practically makes a point of insertion of the diaphragm upon the gall bladder and adjacent margin of the liver. The diaphragm overlying the mound bounded by grooves 3 and 6 shows by transmitted light alternate thick and thin areas; the former, rather wide bands lie in grooves 4 and 5, the latter correspond to the eminences between these four sulci. The thinning suggests that the thickening is due in part to the migration of intervening fibers, not alone to hypertrophy. There is no modification of the region of the diaphragm in relation to 1 and 2. There are no tubercular nodules in the lungs and the only indications of pleurisy are slight adhesions near the apex of the right lung; but a localized peritonitis in the right hypochondrium has resulted in adhesions between the right lobe of the liver and the diaphragm in addition to the strong adhesion already mentioned (Fig. 6).

One other liver is of interest because it has a suggestive appearance early in fœtal life. Taken from a fœtus of three and a half months, this liver, normal in other respects, has on its ventro-lateral border a slight bomb, limited mesad by a broad shallow groove; while on the superior and lateral surfaces is a series of linear impressions which correspond to alternate thick and thin longitudinal bands in the diaphragm.

Through the kindness of Dr. Kerr of Cornell University,

it is possible to report on 16 additional grooved livers (page 373). The source, preparation, age, and sex of the bodies from which these came are much the same as that of material used in this laboratory. These livers like those already described show a great variety of form and of grooves. Six of them are small, about the size of the His model, four medium, six large, but none are much enlarged. Six of these, 37 per cent, have only one groove. This coincides with the conditions existing in the first series and indicates that single grooves are not so rare as claimed by some authors.

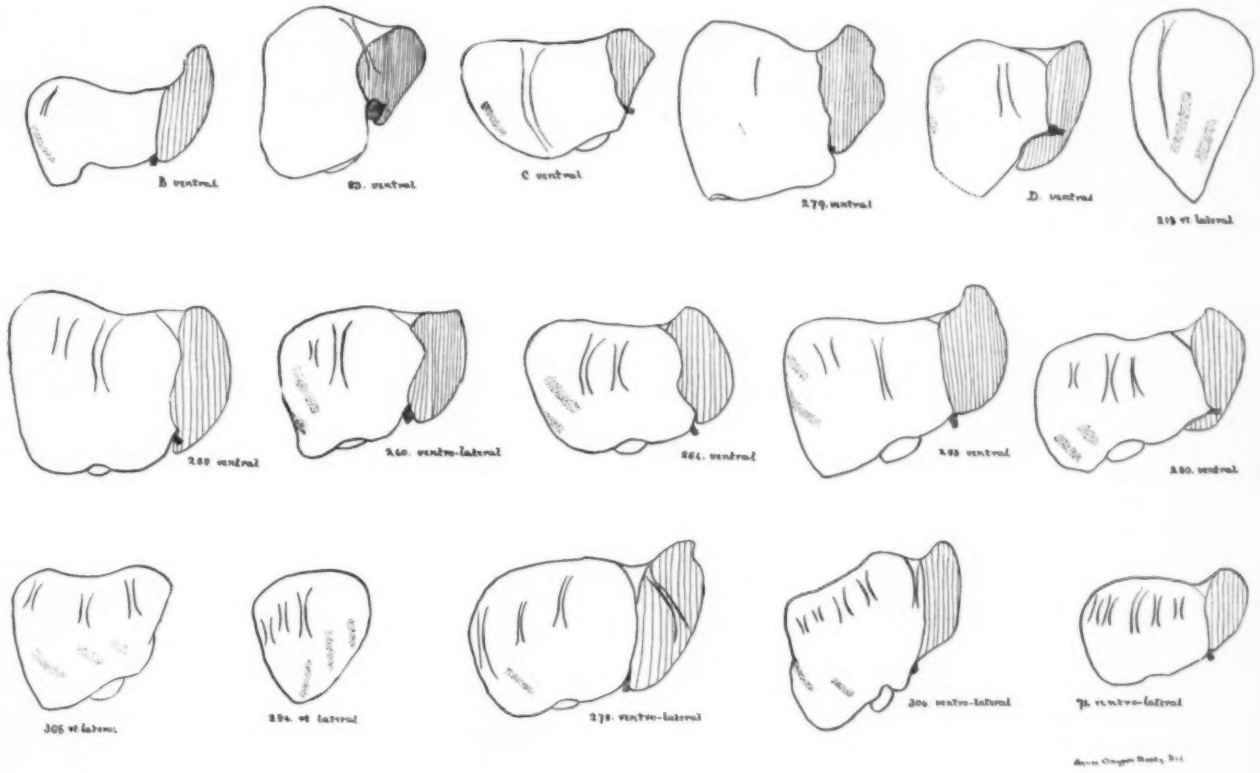


Table 2 gives most of the facts of interest concerning these livers but numbers 83, 278, 71, and 254 show some features that should be especially mentioned. Number 83 is unique in that its single diaphragmatic groove passes from the right lobe to the left across the falciform ligament; 278 has one of its four grooves entirely on the left lobe. The diaphragm in number 71 is still attached to the liver by the coronary ligament and shows alternations of thick and thin bands in the musculature which seem to be mainly due to a readjustment in position of the muscle bundles rather than to hypertrophy. The thicker bands correspond to the grooves and the thinner areas to the eminences. Number 254 had in groove 1 a part of a diaphragmatic fold, the inferior end of which was adherent to the surface of the liver. This suggests a causal relation between a localized peritonitis and the grooves similar to that found in 151.

General Summary.

From the foregoing descriptions and accompanying figures (page 369) it can be seen that grooves occur on livers varying much in form. Some resemble the His model, others belong to one of Charpy's extreme types, the flat, in which the dorsal and inferior surfaces are in one plane; the bomb or dome-shaped which he considers pathological. They vary in size from a liver much enlarged to one distinctly below the adult average. The right lobe is normal, elongated in a longitudinal or transverse direction, thickened or flattened and is frequently bomb-shaped; the bomb is directed ventrad, cephalad, or laterad or in intermediate directions.

The left lobe is usually normal but in one case nearly equals the right in length and twice reaches to the left lateral abdominal parietes. The Spigelian lobe is pinched and elongated in but one case, the gall bladder in two; in one instance both make an acute angle with the long axis of the body.

Mattei's (1890) record, together with that made here, should alone be used in estimating the frequency of grooved livers, as others fail to give the total number of subjects ex-

the tanks have that position best suited to advantageous use of the space. Of the adult subjects received here about 79 per cent are old males, 7 per cent old females, 13 per cent young males, 1 per cent young females. The fœtal material is preserved either in alcohol or formalin; the 2 subjects in which grooved livers were found, were in alcohol.

The great variety of size and form found among these livers as shown on page 369 made it convenient to group them for description according to the number of grooves present; also for convenience the sulci are numbered from right to left.

Livers with One Groove.

Of these there were six, five adult, one fœtal; three male, one female, two unknown. They differ widely as to form, weight, size, and character of the sulcus. Of the entire series X approaches most nearly to the form and size of the His model, the differences between them being no greater than may exist between any two normal livers. It is not bomb-shaped nor deformed in any other way, its only peculiarity being a moderately deep, curved, slit-like furrow on its ventral surface.

In extreme contrast to this is A, which shows a condition usually considered uncommon but present to some degree in 9 of these cases; this liver lying almost wholly in the right hypochondrium, has an unusually broad lateral surface and the so-called dorsal surface looks mesad. The organ is much enlarged and the right lobe elongated; it is marked by two faint costal impressions and on the lateral surface by a long, wide, moderately deep, diaphragmatic sulcus extending vertically. A marked bomb projects upward and forward, bounded laterally by the sulcus.

Subject 89, a liver of moderate size having the right lobe much elongated, the Spigelian lobe and gall-bladder both pinched and elongated, also lies mainly in the right hypochondrium. It is so flattened that the dorsal and inferior surfaces lie in one plane, which looks mesad. There are three costal impressions and on the lateral surface one faint sulcus which is broad and very shallow. There is a strong resemblance between 89 and 104, the next to be described. This too is narrowed transversely and lies chiefly in the right hypochondrium, its much elongated right lobe extending into the right lateral abdominal region; the gall bladder is elongated but the Spigelian lobe is normal in form. The dorsal and inferior surfaces lie in the same plane and look mesad. A well-marked bomb projects from the ventro-lateral border, just laterad of which is a wide, rather deep groove; two costal impressions lie dorsad of the groove.

Of moderate size, not elongated, situated entirely in the right hypochondrium, except for the small flattened extremity of the left lobe, 48 is peculiar on account of a distinctly fœtal position of the gall bladder, which lies in a fossa terminating three centimeters from the inferior border of the right lobe. As in the three preceding livers the dorsal and inferior surfaces lie in the same plane and look mesad. A distinct bomb is seen on the ventro-lateral border. On the lateral surface close to the dorsal border, extending upon the superior surface and containing a fold of the diaphragm is a long, deep sulcus, very narrow at the bottom, spreading at the top; costal impressions groove the dorsal border. In this subject, a male of 43 years, the diaphragm is firmly adherent to the liver between the leaves of the coronary ligament and to the chest wall as high as the fifth interspace, a little laterad of the nipple line and as high as the ninth rib in the mid-axillary line; it is also firmly adherent to the base of the right lung. On the superior surface there is no indication of the fold running nearly parallel with the 8th rib so distinctly seen on the ventral surface. The pleural surfaces of the fold are firmly bound together by adhesions which are continuous with a thickened mass of scar tissue covering a large area in its vicinity. Both the musculature in the fold and the underlying peritoneum are distinctly thickened. The lungs are tubercular, the right being firmly adherent to the chest wall and to the diaphragm over a large area surrounding the fold. Another abnormality in this subject was a bilocular stomach. The last of this group, 120, is the liver of an eight months' female fœtus; it appears normal in every way except for a faint, broad, shallow sulcus on the ventral surface near the lateral border.

Livers with Two Grooves.

Of the livers with two grooves 80 is moderate in size, lies chiefly in the right hypochondrium, has a prominent bomb projecting from the ventral and lateral surfaces. This is bounded laterally by a long, wide diaphragmatic groove of considerable depth, reaching from the superior surface to near the inferior margin, and carries on its summit a faint, shallow sulcus. The lungs in this subject, a male 78 years of age, were normal with slight lateral pleuritic adhesions. The inferior surface in this liver is distinct from the dorsal which looks nearly mesad.

From an adult female subject, 103, the liver is of moderate size, somewhat elongated transversely, has two costal impressions and a small bomb directed ventrad. The dorsal and inferior surfaces are in one plane and look dorsad. Of the two diaphragmatic grooves the deeper, shorter and broader, lies on the ventral surface of the right lobe; the other very faint, is on the ventro-lateral border. The lungs showed no indications of disease; the right lung, however, had five lobes and was slightly adherent to the diaphragm.

The next specimen, 115, is most interesting because it is distinctly grooved and occurred in a male fœtus of about 9 months. The liver is in other respects approximately normal except for some post-mortem depressions and curling of the edges. The broader of the two grooves, 1.9 centimeters long, .15 centimeters deep, with widely diverging sides, is placed on the ventro-lateral border and is parallel to the falciform ligament and to the overlying muscular fibers of the diaphragm. The other groove situated a little mesad of the first on the ventral surface is 1.7 centimeters long, shallow, wide and directed obliquely so that the superior extremities

of the two grooves if continued would meet within a short distance. The muscular fibers of the diaphragm lying in this groove are parallel with it. There are no indications of thickened bands or thinned areas in the diaphragm, but a part of its tendon lies in the cephalic end of the longer groove (Fig. 3).

Livers with Three Grooves.

Liver 76 is flattened so that the inferior and dorsal surfaces are in one plane which looks dorso-mesad. It has two faint costal impressions and near the ventro-lateral border a small bomb. The sulci vary widely as to size and form; number one lying on the lateral surface near the dorsal border is short, wide and very shallow. Two, about a centimeter mesad of one, is 8 centimeters long, .5 centimeters wide at the bottom and 1.4 centimeters deep with widely divergent sides. The third, on the summit of the bomb, is 8 centimeters long, 1.8 centimeters deep and very narrow, its almost perpendicular sides making a sharp contrast with those of the other grooves. The great omentum, tucked up between the liver and the diaphragm and adhering to both, filled the two wide grooves and covered the narrow one without dipping into it, excluding the diaphragm from any close relation with the furrows. The pleura of both lungs was more or less adherent to the chest wall but not to the diaphragm (Fig. 4).

Like the preceding, this liver, 105, has its dorsal and inferior surfaces in one plane that looks dorso-mesad. It lies chiefly in the right hypochondrium and has two very faint costal impressions; there is no general enlargement nor projection into a bomb. The first groove situated on the dorsal border is very faint. The second, the most distinct, lies near it on the lateral surface; the third, very broad and shallow, is ventral. They are all parallel with the overlying fibers of the diaphragm which fits into them but has no permanent folds. In the neighborhood of the sulci there were on the diaphragm three thin areas alternating with two bands equal in thickness to the rest of the musculature but appearing thicker. The thorax had been cut in the median line, rendering it impossible to determine whether the thinned areas correspond with the grooves or with the ridges between them.

Enlarged in all its dimensions, 112 has a right lobe extending 3.5 centimeters below the costal border, a slight bomb on the ventro-lateral margin, and the peculiar flattened superior surface mentioned by Liebermeister which forms a right angle with the ventral surface. The Spigelian and quadrate lobes and the gall bladder are not, as customary, parallel with the falciform ligament but lie at an angle of 45 degrees to it. The dorsal and inferior surfaces are in one plane directed dorsad. The extremity of the left lobe is much flattened and elongated so that it overlaps the spleen and is in contact with the left parietes. A very shallow sulcus situated near the dorso-lateral border extends over the superior upon the dorsal surface. Two centimeters mesad is a second, passing over the same surfaces and curving so as to meet the preceding groove on the dorsal surface; its lateral portion is deep with widely diverging walls, its superior shallow, its dorsal slightly deeper. The third sulcus, 1.8 centimeters deep, .7 centimeters wide, parallels the second on the lateral and superior surfaces and has nearly vertical walls. All the sulci lie laterad of the bomb and are depressions below the normal surface of the liver; they are not longitudinal but oblique, their inferior extremities making an acute angle with the long axis of the body. Grooves two and three lodge diaphragmatic folds which exactly fill them. The adjacent pleural surfaces of these folds are firmly united by old adhesions, giving the cylindrical reliefs described by Tigri (1873). A thick layer of organized scar-tissue formed by pleuritic adhesions concealed any sign of the groove on the superior surface. The fold lying in groove three passes obliquely from the 8th to the 11th costal interspaces; number 2 passes from the inferior border of the 9th rib over the 12th, its fibers continuing into the right crus. Owing to the adhesions on the right side between the pleura of the thoracic wall and the diaphragm, the line of insertion of the latter was permanently changed to a higher level, corresponding very closely laterally and ventrally to the outline of the lung in expiration. These folds hardened in situ proved on microscopic examination to be the simple infoldings of the diaphragm and its pleura with a thick overlying mass of scar-tissue. The musculature of the folds was thickened. Tubercular nodules were present in both lungs and the pleura was extensively adherent to the thoracic parietes and diaphragm, especially on the right side and in the region of the folds (Fig. 5).

Livers with Four Grooves.

The first of this group, 119, from a male aged 76, is normal in size and shape except that the inferior and dorsal surfaces lie in one plane looking dorsad. The grooves present two distinct types, the deep slit and the shallow groove, the one with parallel and the other with widely diverging walls. These appear on surfaces which do not rise above the normal level, that is, the sulci are depressions of the liver substance. Groove one, a mere slit 1.5 centimeters long, lies on the lateral near the superior surface; the second of the same length but broader is on the ventro-lateral border, the other two shallow with widely diverging walls are on the ventral surface.

The next, 40, from a male subject 43 years old, is large, the right lobe not elongated, the left extending to the edge of the spleen. There is a bomb of large lateral but slight ventral projection; the grooves, 2 on the lateral and 2 on the ventral surface, are shallow, parallel, slightly converging superiorly, with widely diverging walls. The diaphragm is somewhat adherent to the liver over the right lobe, but has no indication of folds.

Livers with Five Grooves.

A moderate ventral bomb, a somewhat elongated gall bladder, the dorsal and inferior surfaces forming one plane and the presence of grooves, distinguish liver 85 from the normal. Sulci 4 and 5 lie on the bomb, 3 bounds it laterally, 1 and 2

are on the lateral surface, 3 and 4 converge toward the superior surface and are long and deep with steeply sloping sides.

Although the next subject, 201, a male aged 80, was embalmed lying on the right side, the liver is not noticeably different from some of the preceding. The left lobe is elongated, nearly equal to the right in length and is flattened dorso-ventrally. The right, not elongated, with distinct dorsal and inferior surfaces, has 2 costal impressions and a slight lateral bomb on the summit of which is a short groove slit-like at the bottom, wide at the top, containing a permanent fold of the diaphragm which crosses obliquely the 8th and 9th ribs. The other grooves, one dorsal and three ventral, are wide and shallow without permanent folds. Except for slight adhesions of the left lung to a portion of the thoracic wall and to the diaphragm, there are no indications of diseased lungs or pleura. The diaphragm hardened in situ shows on microscopic examination that the fold consists of a thickening of the musculature only, the pleura passing smoothly over the fold. There is no thickening of the diaphragm overlying the shallow grooves, the directions of which correspond to that of the muscular fibers.

Liver with Nine Grooves.

The last adult case, 151, a female 78 years old, presents a number of interesting conditions. The liver which resembles the fœtal type in the nearly equal size of the right and left lobes and in its position in the epigastric and both hypochondriac regions, is unusually short and broad and so flattened that the dorsal and inferior surfaces lie in one plane directed dorsad. It is marked by 9 diaphragmatic grooves, 6 on the right and 3 on the left lobe. The only other liver with 9 sulci, reported by Meckel (1812) had this arrangement reversed. Groove 1, shallow, short and broad, is about 2 centimeters from the right lateral border. Two, similar in size and shape, is about 4 centimeters from the border. Three, a little further mesad, is long, deep, concave toward the falciform ligament, with parallel walls which slope from the opening of the groove dorsad and slightly mesad. This forms the lateral boundary of an oval mass of liver substance 9 centimeters long, 7 centimeters wide, which projects slightly beyond the adjacent surface and bears on its summit two well-defined sulci. The other boundary is groove 6, long, narrow, and concave laterad; its walls are not parallel, the one next to the mass is directed dorso-dextrad and the other is almost parallel with the ventral surface of the liver. The planes of grooves 3 and 6, if prolonged would intersect within a short distance. The left lobe has a large, flat, superior surface separated from the ventral by a distinct angle and a well-marked splenic impression on its dorsal surface. The remaining three grooves are on this lobe. Seven, close to and parallel with the falciform ligament, moderately broad and shallow, is for the greater part of its length on the ventral surface but extends upon the superior, where it curves, sinistrad. Groove 8 lying entirely on the ventral surface about 5 centimeters from 7 is very shallow and is directed obliquely toward the median line. The last of these sulci, about 2.5 centimeters from the left lateral border, parallel to it and the preceding groove, is the most distinct on this lobe and lies on both the superior and ventral surfaces.

The gall bladder contains an oval stone, the axes of which are respectively 4.7 and 3.7 centimeters in length. That part of the ventral surface of the gall bladder extending beyond the inferior border of the liver is firmly adherent to the diaphragm over an area measuring 2.5 x 3.5 centimeters.

In situ the diaphragm shows distinct folds corresponding to grooves 3, 6, 8, and 9, which disappear on its removal from the body. The crests and sides of the folds lying in 3, 6, and 9 are formed by thickened bands of musculature not flanked on either side by thinned areas, thus indicating that the thickening is possibly due in part to hypertrophy, not alone to sliding of the muscle fibers. In the region of 9, the diaphragm is thickened over an area greater than that indicated by the groove. The fold itself is also longer and deeper than the underlying sulcus, which points to the formation of the fold prior to the groove. The folds corresponding to grooves 3 and 6 converge superiorly and terminate independently at the tendon on either side of the vena cava. Superiorly they also converge and unite in the thickened area of adhesion between the gall bladder and the diaphragm. Notwithstanding this unusual convergence at the periphery, the folds are parallel with the musculature. The changed direction of the muscle fibers is due primarily to a cholecystitis resulting in an adhesion of the gall bladder to the diaphragm and subsequent formation of scar-tissue, which by thickening and contraction tends to draw together fibers within the area of its influence. This practically makes a point of insertion of the diaphragm upon the gall bladder and adjacent margin of the liver. The diaphragm overlying the mound bounded by grooves 3 and 6 shows by transmitted light alternate thick and thin areas; the former, rather wide bands lie in grooves 4 and 5, the latter correspond to the eminences between these four sulci. The thinning suggests that the thickening is due in part to the migration of intervening fibers, not alone to hypertrophy. There is no modification of the region of the diaphragm in relation to 1 and 2. There are no tubercular nodules in the lungs and the only indications of pleurisy are slight adhesions near the apex of the right lung; but a localized peritonitis in the right hypochondrium has resulted in adhesions between the right lobe of the liver and the diaphragm in addition to the strong adhesion already mentioned (Fig. 6).

One other liver is of interest because it has a suggestive appearance early in fœtal life. Taken from a fœtus of three and a half months, this liver, normal in other respects, has on its ventro-lateral border a slight bomb, limited mesad by a broad shallow groove; while on the superior and lateral surfaces is a series of linear impressions which correspond to alternate thick and thin longitudinal bands in the diaphragm.

Through the kindness of Dr. Kerr of Cornell University,

it is possible to report on 16 additional grooved livers (page 373). The source, preparation, age, and sex of the bodies from which these came are much the same as that of material used in this laboratory. These livers like those already described show a great variety of form and of grooves. Six of them are small, about the size of the His model, four medium, six large, but none are much enlarged. Six of these, 37 per cent, have only one groove. This coincides with the conditions existing in the first series and indicates that single grooves are not so rare as claimed by some authors.

tween a localized peritonitis and the grooves similar to that found in 151.

GENERAL SUMMARY.

From the foregoing descriptions and accompanying figures (page 369) it can be seen that grooves occur on livers varying much in form. Some resemble the His model, others belong to one of Charpy's extreme types, the flat, in which the dorsal and inferior surfaces are in one plane; the bomb or dome-shaped which he considers pathological. They vary in size

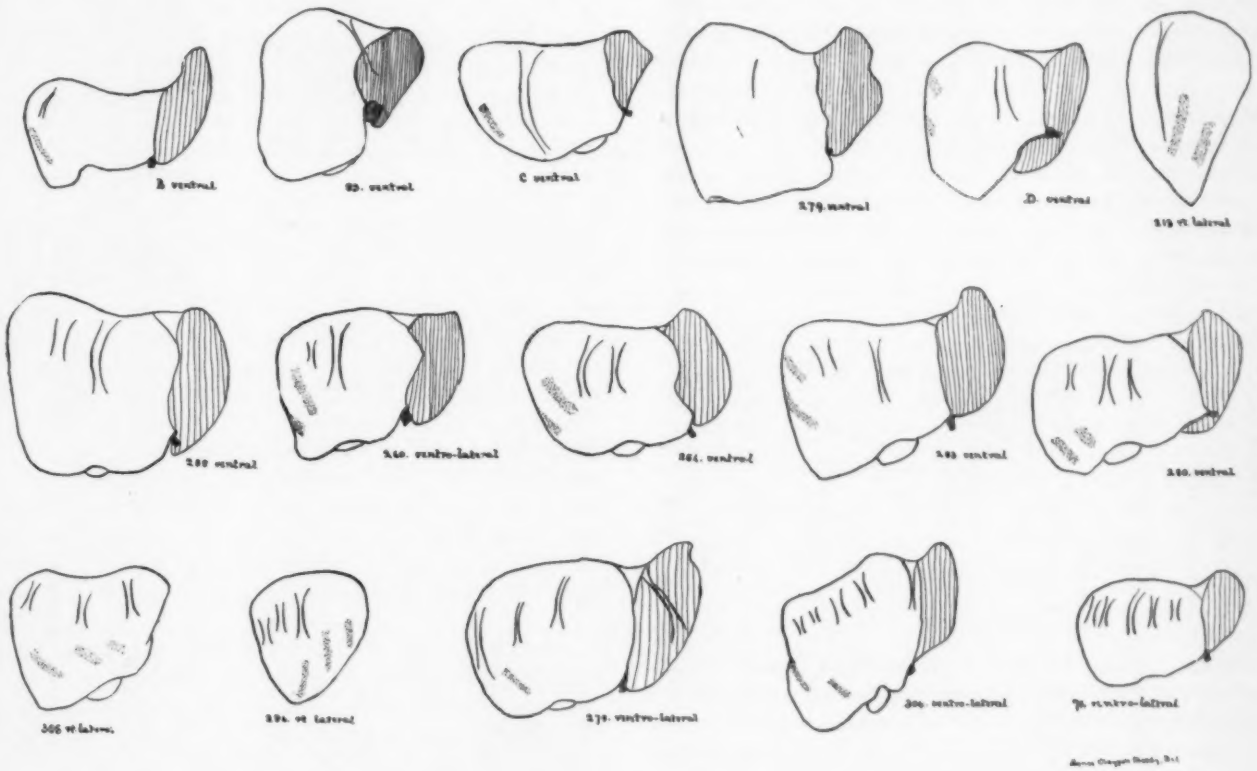


Table 2 gives most of the facts of interest concerning these livers but numbers 83, 278, 71, and 254 show some features that should be especially mentioned. Number 83 is unique in that its single diaphragmatic groove passes from the right lobe to the left across the falciform ligament; 278 has one of its four grooves entirely on the left lobe. The diaphragm in number 71 is still attached to the liver by the coronary ligament and shows alternations of thick and thin bands in the musculature which seem to be mainly due to a readjustment in position of the muscle bundles rather than to hypertrophy. The thicker bands correspond to the grooves and the thinner areas to the eminences. Number 254 had in groove 1 a part of a diaphragmatic fold, the inferior end of which was adherent to the surface of the liver. This suggests a causal relation between a localized peritonitis and the grooves similar to that found in 151.

from a liver much enlarged to one distinctly below the adult average. The right lobe is normal, elongated in a longitudinal or transverse direction, thickened or flattened and is frequently bomb-shaped; the bomb is directed ventrad, cephalad, or laterad or in intermediate directions.

The left lobe is usually normal but in one case nearly equals the right in length and twice reaches to the left lateral abdominal parietes. The Spigelian lobe is pinched and elongated in but one case, the gall bladder in two; in one instance both make an acute angle with the long axis of the body.

Mattei's (1890) record, together with that made here, should alone be used in estimating the frequency of grooved livers, as others fail to give the total number of subjects ex-

TABLE II.

No. of subject.	Sex.	Age.	No. of grooves. Costal.	No. of grooves. Diaph.	Depth. 1. 2. 3. 4. 5. 6. 7. 8. 9.	Length. 1. 2. 3. 4. 5. 6. 7. 8. 9.	Breadth. 1. 2. 3. 4. 5. 6. 7. 8. 9.	Position. 1. 2. 3. 4. 5. 6. 7. 8. 9.	Sides. 1. 2. 3. 4. 5. 6. 7. 8. 9.	Direction of bomb. Superior.	Ventral.	Lateral.	Right lobe elongated.
X	?	?	0	1	.35	3.6	s.	v.	p.				0
A	?	?	2	1	1.	7.5	.35	l.	w. d.	+	+		+
48	♂	43	3	1	1.8	10.	.1	l.	m. d.	+	+		0
89	♂	62	3	1	—	—	—	l.	—		+		+
104	♂	51	2	1	1.	6.8	—	l.	w. d.	+			+
120	♀	*	0	1	—	—	—	v.	—				0
80	♂	78	0	2	1.4 .1	10.7 2.2	.35 —	l. v.	m. d. —		+		0
103	♀	53	2	2	— .3	— 4.	— .7	v. l. b. v.	— w. d.		+		0
115	♂	**	0	2	1.5 —	1.9 1.7	.2 —	v. v.	w. d. w. d.				0
76	♂	64	2	3	.1 1.4 1.8	4.3 8. 8.	— .5 —	l. l. v.	— m. d. p.		+		0
105	♂	68	2	3	.1 .35 .05	2.5 3.3 3.5	— .2 —	d. b. l. v.	— w. d. —				0
112	♂	70	3	3	.2 .9 1.8	8.2 10.9 7.5	— .52 .7	l. l. l.	— m. d. p.	+			+
40	♂	old	2	4	.2 .4 .25 .1	5.5 6.1 6.2 3.1	— — — —	l. v. l. b. v. v.	w. d. w. d. w. d. w. d.		+		0
119	♂	76	1	4	s. .3 .3 .5	1.5 3.7 3.8 4.2	s. .15 — .2	l. v. v. v.	p. m. d. w. d. w. d.				0
85	♂	73	0	5	.4 .4 1.2 1.4 .1	5.1 4.3 7.7 8.1 3.5	.2 .28 .28 .38 —	l. l. l. v. v.	w. d. w. d. m. d. m. d. —		+		0
201	♂	80	0	5	— .7 — .1 .3	2. 5. 2. 1.5 4.5	— .05 — — —	d. l. v. v. v. left lobe.	w. d. m. d. w. d. w. d. w. d.			+	0
151	♀	78	0	9	— — 1.7 .1 .4 1.9 — — .3	3.8 4.6 8.5 4.6 6.1 6.6 4. 3.7 3.9	— — .3 — .25 .5 — — —	v. v. v. v. v. v. v. v. v.	w. d. w. d. p. w. d. m. d. m. d. w. d. w. d. m. d.				0
B	?	?	3	1	.6	3.5	—	v. l.	s.				0
80	♂	51	1	1	1.	3.2	—	v.	w. d.			+	+
C	?	?	2	1	2.	9.5	.2	v. l.	p.				0
279	♂	68	0	1	1.	2.5	s.	l.	s.				0
D	?	?	3	1	.4	5.	s.	v.	w. d.				+
213	♂	80	2	1	1.5	10.1	3.	l.	p.				0
258	♂	68	0	2	— —	6.5 7.	— .2	l. l.	— w. d.		+	+	0
260	♂	40	2	2	1.5 .5	4.7 4.7	— .2	l. l.	w. d. m. d.		+	+	+
254	♂	77	2	2	1.5 1.	9.5 9.7	.5 .2	l. l.	p. m. d.		+		0
283	♂	84	2	2	— .5	4.5 8.	— —	v. l. v.	— m. d.				0
280	♂	85	2	3	.2 .8 .6	2. 7.7 6.1	— .35 .1	l. l. l.	w. d. p. p.				0
305	♂	?	3	3	.4 .6 1.1	7.2 6.8 6.	.2 .35 .25	d. l. l.	w. d. w. d. w. d.			+	0
286	♂	76	3	4	.1 .2 .8 —	5.5 5.7 8.7 5.	.2 .25 .25	d. d. l. d. l. v.	w. d. w. d. m. d. w. d.		+	+	0
278	♂	64	1	4	.1 .2 .1 .3	4.5 3.7 2.5 8.1	— — — .35	d. l. l. l. v.	— w. d. w. d. —		+	+	0
304	♀	71	2	5	— — .6 .2 .8	3. 2. 5.2 3.5 5	— — 2.5 .2 —	l. l. l. l. v.	— — w. d. w. d. w. d.	+	+		0
71	♂	60	0	6	1. .6 .6 .5 .3 —	3.7 4.2 4.6 4.6 4 —	— .2 .2 .2 — —	l. l. v. s. v. s. v. s.	— m. d. w. d. w. d. w. d.			+	0

* fœtus 8 months.
** fœtus at term.
d. = dorsal.
d. b. = dorsal border.
d. l. = dorso-lateral.

l. = lateral.
m. d. = moderately diverging.
p. = parallel.
s. = slit.
v. = ventral.

v. s. = ventro-superior.
v. l. = ventro-lateral.
v. l. b. = ventro-lateral border.
w. d. = widely diverging.

— = too small or too indefinite for exact measurement.
+ = position of bomb or elongation of right lobe.

amined. Adding to his 146 bodies the 68 examined here gives a total of 214, in which 86 grooved livers were found, that is, they occurred in 40 per cent of the bodies. This result will probably be changed when systematic records of thousands instead of hundreds of cases are available. The same limited records give the only adequate data for the determination of sex frequency. The accompanying tabulation shows that grooved livers were found in 53 per cent of the females and 27 per cent of the males. The absolute accuracy of this percentage is further limited by the small number of female subjects autopsied or dissected.

TABLE III.

	Bodies examined.		Grooved livers found.	
	Male.	Female.	Male.	Female.
Mattei	87	59	26	35
Moody	59	9	13	2
	146	68	39	37

Table 2 shows that grooves are found on the ventral surface of the right lobe 30 times, on the lateral 37, dorsal 3, ventro-lateral border 5, dorsal border 1, dorso-lateral border 3, ventro-superior 3. Some of these grooves pass to the superior surface, a few extending upon the dorsal. In two livers, 43 and 151, grooves occurred on the ventral surface of the left lobe and in one, 83, a groove passed from the right to the left lobe. Approximately parallel to each other and to the long axis of the body, the grooves usually have the direction of the overlying muscle fibers and consequently tend to converge at the top and diverge at the bottom. In a single case, 112, one ventral and one lateral groove converged to meet on the dorsal surface. Even in 151 where the two deep grooves converge at both ends the fibers coincide in direction.

The same table also shows that of the 33 grooved livers, 23 were found in adult males, 3 in adult females, 1 in a male, and 1 in a female fœtus, 5 in bodies of which no record was kept. It also shows that most of the subjects are old; 4 between 80 and 90, 5 between 70 and 80, 7 between 60 and 70, 3 between 50 and 60, 2 between 40 and 50. No subjects in youth or infancy are available and only 14 fœtuses. Of the latter there are seven of each sex, their ages ranging from 15 weeks to nine months. Distinctly grooved livers occur in an 8 months' female and in a 9 months' male fœtus and in a 3½ months' female there is a slight bomb and a strong suggestion of furrows. The number of grooves varies from 1 to 9 but, contrary to Buy's observations in which two and three sulci were most common, one occurs most frequently in the adult series. The tabulation shows depth to vary from less than 1 to 19 millimeters but indicates no such relation between depth and position as is suggested by Buy and Jacquemet nor does it show such a constant increase of depth with age as is claimed by Mattei and Buy. The deepest groove occurs in various positions with reference to the others. There is no constant relation between depth, breadth and length, although in general the deepest are longest and narrowest. The length varies from 1.7 to 10.9 centimeters, the bottom breadth from a mere slit to .7 centimeters. In a large proportion of cases the breadth of the grooves increases at the top by the divergence of the walls which sometimes is so great that in shallow grooves no measurements are practicable.

Since the peritoneum is not preserved in embalmed material, its condition cannot be ascertained, but in five cases in which microscopic examination has been made the capsule at the sides and bottom of the groove is thickened, slightly in the shallow and greatly in the deep grooves. Blood-vessels, larger than those usually found, lie in this thickened connective tissue. The parenchyma is degenerated and atrophied at the sides and bottom of the grooves; this process has extended in some cases to include the peripheral layer of liver lobules.

Besides these microscopic changes certain gross pathological conditions are found involving the lungs, pleura, stomach and liver. Owing to the fact that dissection was more or less advanced when the grooves were first noticed, observations on organs other than the liver are not complete. In seven cases the condition of the lungs is recorded, in four of which they were normal, in three tubercular. Eight cases were examined for pleurisy; it was found double in seven, single in one, slight in six, and in three the pleura is adherent to the diaphragm. A bilocular stomach occurred in one case in which there was also a double ureter on the right side. Of the so-called "signs of constriction" the superior bomb is present in 5 cases, the elongated right lobe in 3 of these and 4 others, costal impression in 23, pinched and elongated Spigelian lobe in 1, elongated gall-bladder in 2. Of the 33, 20 have bombs,[4] 7 ventral, 2 superior, 3 lateral, 3 ventro-superior, 5 ventro-lateral; the 12 without bombs include fœtal livers.

REMARKS.

The custom of generalizing from a few cases and the desire to establish a certain hypothesis has heretofore often resulted in limiting the horizon of observers and in coloring their interpretations of facts. It is evident that this study can yield no theoretical generalizations, but it suggests some new possible causes in certain cases and presents some interesting evidence which modifies previous interpretations.

In only one case are the grooves so situated that they could possibly be formed by the lower margin of the ribs as demanded by Liebermeister's (1864) theory; moreover in four of the cases there are no lesions of the lungs or pleura that would cause forced respiration. The latter fact has equal weight against Zahn's (1882) view and, as Buy (1904) has pointed out, diaphragmatic folds or digitations are not always present, a condition incompatible with Zahn's (1882) state-

[4] A modification is made of Charpy's term "bombé" which he applies only to livers decreased in transverse and dorso-ventral diameters with a superior protuberance. In these tables and descriptions its use is extended to include livers with lateral and ventral projections.

ment that they must precede the formation of grooves. Further, as Mattei (1890) claimed and Orth (1888) and I have demonstrated, these grooves exist in intra-uterine life.

The occurrence of the sulci on fœtal livers and the presence in adults of thickened muscular bands at the bottom of the grooves and thinned areas over eminences are the only facts found to support Mattei's (1890) theory, but this condition loses its significance when it is remembered that in some of the adult and fœtal subjects the musculature of the diaphragm is of uniform thickness. The existence of grooves without folds is further evidence against this view and moreover if Mattei (1890) is right the eminences are always above and the bottom of the grooves at or slightly below the normal level of the liver surface; whereas in cases 112, 119 and 115 the summits of the mounds are not above this level. Again, in several cases there are in the diaphragm alternate thick and thin bands, which are so far distant from the grooves, that no causal relation can possibly exist. The other theory considering the grooves to be of congenital origin, advanced by Tigri (1873) and based on only three cases, fails to account for those instances in which folds are absent.

A careful consideration of the facts in these cases shows that the constriction theory may account for some but entirely fails when applied to others. Table 2 apparently supports Buy's (1904) claim that grooves occur chiefly in old people but it should be remembered that comparatively few subjects in infancy or youth come to the dissecting or autopsy tables. His statement that grooves are much more frequent in females than in males is also seemingly confirmed but the same fallacy exists in these as in Mattei's (1890) results, that the total number of female bodies examined is comparatively so small that the result does not necessarily indicate the facts. The absence of folds and the evident heaping of the liver tissue in some cases gives a real support to this theory. Opposed to it are the facts that grooves occur upon 4 livers bearing no marks of constriction, and that five livers with acknowledged characters of long continued constriction have no diaphragmatic grooves. Of the constriction signs, designated by Buy (1904) as constantly coexisting, the elongated right lobe is found in only six cases; costal grooves, which may be post-mortem in 23, and a bomb in 19, bilocular stomach once; elongated gall bladder twice and a similar condition of the Spigelian lobe once. But splenic costal grooves, enteroptosis, nephroptosis, transformation of some part of the left lobe into membranous appendices and a partial separation of the caudal extremity of the right lobe are not found. The one insurmountable obstacle to the general application of the constriction theory is the existence of diaphragmatic grooves on fœtal livers. Three such cases are now on record; the youngest fœtus, 7 months, is reported by Orth (1888) and the two others are described in this paper together with the liver of a 3½ months' fœtus with strong suggestions of the beginning of such grooves.

The formation of sulci before birth, at a time when there can be no external pressure by clothing and the organs of respiration are yet inactive, excludes the application of both the constriction and disordered respiration theories to these cases; and the associated uniform thickness of the diaphragmatic musculature renders the hypothesis of Tigri (1873) and Mattei (1890) equally inapplicable. A simple explanation suggests itself as possible. It is well known that the size of the teeth is not always proportionate to that of the jaw so that the former are sometimes very much crowded. Thus it is possible that a similar disproportion between the abdominal capacity and the liver might result in a folding of the liver substance and the formation of grooves.

The associated conditions in 112 and 48 suggest another interpretation applicable to some cases. As already described the diaphragm in both subjects was firmly bound to the right thoracic wall and to the pleura of the right lung by strong adhesions which results in a high insertion and consequent shortening of the diaphragm. Microscopic examination of the folds shows thickened pleura, musculature and peritoneum with adhesion of the infolded layers. These conditions indicate that a severe pleurisy has been followed by the development of scar-tissue which in turn contracts and causes a folding of the diaphragm naturally parallel with the long axis of the muscle fibres and a subsequent grooving of the liver by the folds; that is, the probable cause of these grooves is the pressure of diaphragmatic folds formed mechanically as a result of a severe diaphragmatic pleurisy.

The pathological conditions in subject 151 suggest still another cause for the existence of the grooves. In this case, it will be remembered, a cholecystitis was accompanied by a localized peritonitis and the formation of strong adhesions between the ventral surface of the caudal part of the gall bladder and the diaphragm. One result of this adhesion was the shortening of all the muscle bundles passing through it, another the subsequent contraction of the scar-tissue which caused these and adjacent bundles to converge. The shortening of these fibers would probably result in compensatory hypertrophy, giving rise to thickened bands which by pressure gradually groove the liver.

Conclusions.

Diaphragmatic grooves are found in the fœtus as early as seven months, in infancy, in youth and in old age.

The grooves may or may not contain folds of the diaphragm, the latter are sometimes permanent and sometimes disappear when the liver and diaphragm are removed from the body.

The comparatively small number of cases recorded does not justify definite generalizations concerning the frequency of these grooves and the age and sex of subjects in which they are most often found.

Many factors take part in the production of the grooves, some of which may be congenital conditions of the diaphragm, difficult respiration, constriction of the thorax and abdomen by clothing, severe diaphragmatic pleurisy, localized peritonitis and a disproportionate ratio between the size of the liver and of the abdominal cavity.

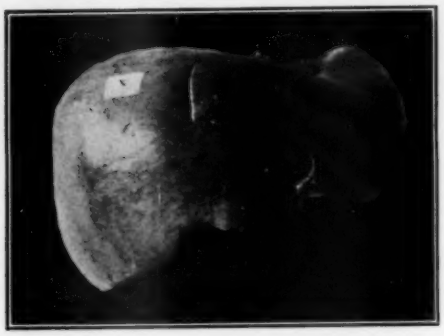


FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

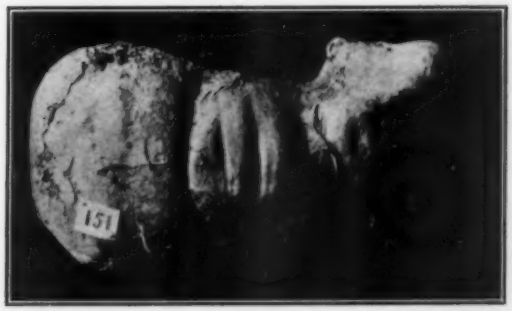


FIG. 6.

BIBLIOGRAPHY.

Bagaloglu, 1899: Bulletin de la Société anatomique de Paris, 67.

Bertelli, 1875: Archivio per le scienze mediche, p. 429.

Buy, J., 1904: Bibliographie Anatomique, Tome 13, 103-123.

Caryophillis, 1889: Bull. de la Soc. Anat. de Paris.

Charpy, A., 1901: Traité d'Anatomie Humaine de Poirier et Charpy, article Foie.

Cornil et Ranvier, 1884: Histologie pathologique, Tome 2, p. 366.

Cruveilhier, J. Anatomie pathologique (Atlas) 29e livraison pl. 4.

——— 1856: Anatomie pathologique générale, Tome 3, p. 209.

——— 1874: Traité d'Anatomie Descriptive, 5 ed. Tome 2, pp. 179-181.

Fernel, 1602: Universae medicae.

Frerichs, F. T., 1879: A clinical treatise on the diseases of the Liver. (transl.)

Glisson, F., 1666: Anatomia Hepatis.

Guéniot, Paul, 1898: Bull. de la Soc. Anat. de Paris.

——— 1899: Bull. de la Soc. Anat. de Paris.

Hayem, 1895: Archives Générales de Medicine.

Jacquemet, M., 1896: Considerations sur les Anomalies du Foie et des voies biliares. Thèse de Lyon.

Klebs, E., 1868-80: Handbuch der pathologischen Anatomie, p. 361.

Liebermeister, C., 1864: Beiträge zur pathologischen Anatomie und Klinik der Leberkrankheiten.

Mall, F. P., 1896: Bull. Johns Hopkins Hospital, Vol. 7, p. 90.

Mattei, R., 1890: Sulle cagione dei solchi diaframmatici del fegato. Sperimentale, Firenze, 64, pp. 232-242.

Meckel, J. T., 1812-16: Handbuch der pathologischen Anatomie.

Michaut, 1888: Bull. de la Soc., Anat. de Paris.

Morgagni, J. B., 1761: De sedibus et causis morborum per anatomem indagatis. Venise.

Orth, Johannes, 1888: Compendium der pathologisch-anatomischen Diagnostik. p. 471, 4th Aufl.

Rathcke, Paul, 1896: Ueber anomale Furchen an der menschlichen Leber. Inaug. diss. Berlin.

Séglas, J., 1886: Note sur les sillons diaphragmatiques due Foie. Bull. de la Soc. anat. de Paris annee 61, p. 163-166.

Soulé, L., 1902: Les Sillons Costaux du Foie. Thèse. Toulouse.

Tigri, A., 1873: Sopra un' anomalia del musculo diaphramma e sulla consequente anormale conformazione del fegato. Roma.

Thomson, A., 1899: The morphological significance of certain Fissures of the Human Liver. Jour. Anat. and Phys., p. 546.

Turner, Sir William, 1898: Quain's Elements of Anatomy. Vol. 3, pt. 4, 10th Ed., p. 128.

Zahn, Wilh., 1882: Note sur les plis respiratoires du diaphragme et les sillons diaphragmatiques du foie. Revue médicale de la Suisse romande, p. 19.

THE RISE OF THE PRESENT CONCEPTIONS AS TO THE CAUSE OF THE HEART-BEAT.

II. THE MYOGENIC THEORY, AND MODERN STUDIES OF RHYTHMICITY.[1]

BY E. G. MARTIN.

The myogenic theory of the origin of the heart-beat, as it stands at the present time, is based on four general points. The first of these is the well-established fact that the property of rhythmicity may reside in muscular tissue entirely independently of the presence of nerve-cells. The second point is the demonstration that certain ganglion-free portions of the adult heart may, by proper treatment, be made to beat rhythmically. The third, and according to Engelmann[2] (Pflüger's Archiv, 1897, Vol. 65, p. 535), the most important fact of all, is the conclusive proof that the whole heart of the embryo contracts rhythmically before it contains the smallest trace of nerve tissue. A fourth fact is that the hearts of many invertebrates are without ganglion cells. A fifth fact, which at the time of its discovery was supposed to be absolutely conclusive, but which has been shown in the light of more recent knowledge to be without particular bearing on the problem, was the observation that in animals poisoned with curare, or as it was known at that time, woorara, the heart continued its beat in the normal manner. This poison was supposed by its first user in physiology, Claude Bernard, to sever completely all connection between motor nerves and the muscles supplied by them. Since it does not affect the heart-beat, the conclusion was at once drawn that the heart-beat is not carried on through the action of motor nerves, and hence must be a property of the muscular tissue itself. I find that special stress is laid on this argument as late as 1875. In Flint's text-book of Physiology, published in that year, the author

[1] Read before the Physiological Seminary of the Johns Hopkins University March 2, 1904.

[2] For complete references to the literature of the myogenic theory of the heart-beat see Engelmann, Pflüger's Archiv, 1897, Vol. LXV, p. 535, et seq.

considers the woorara effect as the most convincing of the facts which he presents in support of the myogenic theory. With the discovery that curare affects only one particular sort of nervous end-connection, a form which is not present in the heart, this argument, of course, lost its force.

To return to the four points, which, as I said at the beginning, are at the present time the strong arguments in favor of the myogenic theory, I have found it a matter of considerable difficulty to prepare an account of their historical development, partly because of the great number of names that are associated with each one of them, and partly, also, because they were foreshadowed in the minds of scientists, so that they are suggested in their writings before the actual proof of their truth had been furnished. I shall attempt, however, to give some idea of the way in which each of them reached its present position.

In the year 1850 Schiff, in an article in the Archiv für physiologische Heilkunde, entitled Der Modus der Herzbewegung, makes the following statements: "Many have held the opinion that all forms of rhythmic activity are accomplished only through the medium of nerve-centers. The various ganglia have been looked upon as such centers, but not only plain muscle, but also cross-striated, skeletal muscles, under certain conditions, after destruction of their central organs, or after section of their nerves, or even after removal from the body, have been observed to make repeated contractions, either rhythmic or arhythmic, just as in the case of the heart. Among these are to be included, not only the periodic contractions of small bits of the diaphragm or of the gills of fishes, which can be seen under the microscope as much as thirty-six hours after the death of the animal, and which were discovered by Remak; but also the strong contractions of the diaphragm which occur for a time after section of its nerves, as described by Valentin; and the intermittent movements of the detached legs of insects and spiders, which can be seen with especial ease in Tipula and Phalangium. In ravens, in which I had destroyed the brain and spinal cord, and separated out the great breast muscle, I have seen, sometimes, the pectoralis minor contract strongly and rhythmically, with such great regularity that after I had determined the interval between the contractions, I could foretell the onset of every one by counting with a watch. These contractions continued after I had separated the muscle, with its adherent portion of the skeleton, from the rest of the body. I cut the ribs, with the intercostal muscles attached, from the body of a young cat, and hung them on a frame. I observed that the ribs, through the rhythmic contractions of the muscles, came together and separated like the slats of a venetian blind. And all these parts, whose rhythmic action was not disturbed by the destruction of their nerves, nor by separation from the body, contained only red, cross-striated muscles, only animal nerve-fibers, with not a ganglion in their substance. Indeed the leg of Phalangium opilio begins its regular movements, and the tail of Lacerta its irregular ones, only at the moment of separation from nerve centers. The heart may well be continuously under just those conditions into which the muscles we have been considering are brought through the experiment, and it can by no means be asserted that the regular rhythm of this organ is necessarily dependent on the existence of nerve centers."

Shortly after the appearance of this paper of Schiff, with its description of the experimental production of muscular rhythmicity, if so his phenomena may be called, statements of the normal occurrence in the animal body of similar muscular rhythmicity began to appear in scientific journals. In 1852 Wharton Jones showed that the veins of the bat's wing contract rhythmically. Schiff, himself, in 1854, described the rhythmic pulsations of the vessels of the rabbit's ear. Several years later, in 1869, Engelmann discovered the fact that the ureters are rhythmically contractile. In each of these cases it was shown, either by the first one to observe it, or by subsequent investigators, that ganglion cells are not present in these tissues. These observations demonstrated beyond question that the power of executing rhythmic contractions may reside in muscular tissue entirely apart from the influence of nerve-cells. While these observations had no direct bearing on the question of the origin of the heart-beat, they were of the very greatest value as indirect evidence, because they made the probability of the muscular origin equal to that of the nervous origin, thus robbing the latter of the greatest advantage it had held up to this time, the proven possibility of nervous rhythmicity, against undemonstrated muscular rhythmicity.

As early as 1858 the observation was made by Eckhard that if a constant current were sent through the apex of the frog's heart, a portion which had been shown to be free from ganglion cells, it would be thrown into rhythmic contractions. Foster and Dew Smith, in 1876, made the same observation. Bowditch, in 1871, and Merunowicz, in 1875, both working in Ludwig's laboratory, showed that the apex of the frog's heart would beat when supplied with a nutrient fluid under pressure. Gaskell, in 1880, proved that a ventricle which had been brought to rest by Bernstein's crushing, could be aroused to activity again by the simple process of clamping the aorta, thus raising the pressure within the chamber. Three years later, in 1883, Gaskell reported that if a strip were cut from the ganglion-free apex of the heart of a tortoise, and suspended under slight tension in moist air, it would begin, after a while, to contract rhythmically, and might remain active for as much as thirty hours. He stated also that the onset of rhythmic activity in an isolated strip could be hastened by the application of stimuli to it at regular intervals. It should be stated that more recent work has not corroborated the statement of Gaskell that strips of heart tissue will develop a spontaneous rhythm when suspended in air without previous treatment, but this modification does not affect his point, which was that the muscular tissue of the heart could be made to beat without the influence of nerves. In 1882 Engelmann showed that the bulbus arteriosus of the frog can be made to beat with great readiness, all that is required being a slight and continuous tension of its walls. He claimed that this part of the heart is without nerve-cells, and

his view seems to find general acceptance, in spite of the fact that one or two observers, Munk (1878), Löwit (1881), and others, have reported their presence. Engelmann also, in 1896, showed that parts of the venous sinus of the frog which are free from ganglion cells could be isolated, and that they would continue to beat for a long time after isolation. As is well known, the normal beat of the heart originates in the region of the great veins, hence, as Engelmann points out, the fact that those parts of them that are not furnished with nerve-cells beat as well as those that contain such cells, is the strongest kind of indication of the correctness of the myogenic theory.

In 1865, A. Brandt, working in St. Petersburg, reported that the hearts of certain crabs, of some species of insects examined by him, and of some molluscs also, are without ganglion cells. The same thing was afterward shown to hold for other invertebrates by Eckhard (1866), Foster (1872), and Foster and Dew Smith (1875).

There remain to be considered in this connection, the facts with regard to the beat of the embryonic heart. It has been a matter of common observation for a very long time that the hearts of embryos, such as the simple heart tube of the unhatched chick, begin to pulsate rhythmically early in the life history of the developing animal. The Weber brothers performed some experiments, such as the effect of variations of temperature and the like, upon the heart tubes of embryo chicks. About their time, the middle of the nineteenth century, the idea began to be entertained that these heart tubes contain no nerves. Such was the indication furnished by the microscope, although with the technique at their command the investigators of that day were unable to prove it. The first positive statement on the subject, which I have encountered, was made by Pflüger in 1877. He found that the heart of the human embryo begins to beat after the third week, whereas no nerve-cells are to be found in it until the fifth week. With the development of modern methods of studying tissues, by means of which every infinitesimal particle of an organ can be scanned with unerring accuracy, the question as to whether or not pulsating embryonic hearts contained nerve-cells, was finally settled. The most complete study of this point was made by W. His, Jr., in 1891. This observer showed that the heart of Scyllium began to beat when the embryo had attained a length of five millimeters, although nerve-cells did not appear until a length of thirteen millimeters had been reached. In the chick the heart-beat after thirty-six hours, while the first indications of ganglion cells appeared only on the sixth day. The upholders of the neurogenic theory explained the beat of the embryonic heart by supposing that embryonic heart tissue was in an undifferentiated form, combining in itself the properties of both muscle and nerve, which properties became gradually separated from each other with the development of the two different adult forms out of the same sort of embryonic substance. His, however, was able to follow the process of development of the embryonic heart, and to demonstrate beyond doubt that all the tissue there present grew into the characteristic, cross-striated muscle substance of the adult heart. He showed, moreover, that the nerve-cells which appear in the heart wander there from the cerebrospinal nervous system. The neurogenists, overthrown in this idea, advanced another argument. They suggested that while it must be admitted that the beat of the embryonic heart is myogenic, there was still good reason to suppose that a transition of control occurs at some point during development, so that the beat of the adult heart becomes nervous. Engelmann points out the difficulty of accepting this proposition, both in view of the fact that the heart, from the very commencement of its activity, beats regularly, without any disturbance such as would inevitably accompany a change in its manner of control, and also in the light of his own observations on the rhythmicity of ganglion-free portions of the great heart-veins.

Gaskell[1] has recently proposed a very satisfactory explanation of the normal sequence of the heart-beat, basing his explanation upon the idea that a distinctive property of embryonic heart tissue is a very high degree of irritability. Let me here quote his own statement of his view. Having called attention to the fact that certain parts of the heart, i. e., the venous sinus, the auriculo-ventricular ring, etc., are more rhythmical than the rest of it, and that this superior rhythmicity has been supposed to be due to the presence in those parts of nerve-cells, he proceeds as follows: "But is there really nothing else peculiar to those parts where rhythm is easiest? If we consider its mode of development, we find that in all vertebrates the heart arises from two longitudinal veins, or venous sinuses, which coalesce to form the sub-intestinal vein and heart; the simple tube so formed, with its circular muscular coat, becomes twisted on itself, and parts of it develop bulgings, the commencement of the auricles and ventricles, in consequence of which the simple circular arrangement of muscle fibers becomes the complex arrangement which is ultimately found. With this special growth of the parts of the tube by which the heart cavities are formed, is correlated a more rapid contraction of the specialized parts of the muscular walls, so as to ensure a more rapid emptying of the separate cavities, and thereby make the heart more efficient as a force pump. The development of this nearer approach to striated muscle is made at the expense of the original rhythmical power, so that finally the muscular tissue of the heart becomes differentiated into muscle of varying rhythmical power, according to the amount of deviation from the original embryonic rhythmical muscle. Those parts which remain least altered, both in the circular arrangement of their fibers and in their physiological status, are naturally the large veins, sinus, and junction of sinus and auricles; then the circularly arranged fibers of the auriculo-ventricular groove; and lastly the conus arteriosus, which represents the final part of the tube beyond the ventricular bulging. In fact, as can be readily understood, if the auricular and ventricular bulgings are special modifications of the muscular tissue, for the purpose of forming rapidly-contracting roomy chambers—in other words, for

[1] Gaskell, Schaefer's Physiol., 1900, Vol. II, p. 177.

the purpose of forming a heart rather than a rhythmically contractile tube—then the very parts which were left unmodified would naturally continue to carry the main intracardiac nerves with their accompanying ganglion cells; so that in the sinus, in the auricles, and in the auriculo-ventricular ring, the ganglionic structures and the less modified muscular tissue would be coterminous." It should be stated that although this idea was developed to its fullest extent by Gaskell, others before him had held the same view. Michael Foster, as early as 1876, made a similar suggestion to explain the greater rhythmic power of the venous portion of the heart.

Only one more point remains to be considered in this immediate connection. It will be recalled that as late as 1894 Kaiser put forth a very strong argument in favor of the neurogenic theory. His argument, to recapitulate briefly, was this. It is well known that if a frog's heart be brought to rest by tying off the sinus, single stimuli applied generally to the surface of either auricle or ventricle are followed by only a single response for each stimulation; whereas, if the stimulus be applied in the region of Bidder's ganglion in the auriculo-ventricular ring, each single stimulation is followed by a series of rhythmic contractions. Moreover, he showed that if Bidder's ganglion were removed, stimulation in the region which before had aroused a series of responses, now, like the structure generally, gives only one response for each stimulus. He drew the conclusion from these results that in nerve centers, such as Bidder's ganglia, and in them alone, resides the power to arouse rhythmic contractions in the heart. The error in Kaiser's argument was brought out by Gaskell,[4] who showed that Kaiser's experiment had not been performed with sufficient care. Gaskell showed that if the ventricle and one auricle in the heart of a tortoise be slit and pinned back in such a manner as to expose fully the inner surface of the septum and auriculo-ventricular ring, together with Bidder's ganglia and the terminations of the vagi in them, the whole of the region about those parts could be explored with a fine-pointed needle. Under these conditions Bidder's ganglia may be pierced with the needle, or pulled upon, or stimulated otherwise as violently as one wishes without arousing a single contraction; but if the muscular tissue of the surrounding auriculo-ventricular ring be touched, never so lightly, a series of rhythmic beats immediately ensues. According to Gaskell's view of the embryonic nature of the auriculo-ventricular ring, which should, as the result of its embryonic nature, retain its property of rhythmicity to a high degree, the result he obtained was the only one to be anticipated. The apparently contradictory result obtained by Kaiser, he explained as due to insufficient care on the part of that observer in limiting his stimuli to the ganglia, in the one case, and in removing the ganglia without at the same time destroying the muscular portion of the auriculo-ventricular ring, in the other.

This work of Gaskell practically completed the chain of evidence in favor of the view that the rhythmic action of the heart does not originate in the ganglion cells. His results, however, apply only to the cold-blooded heart. The proof was extended so as to include the mammalian heart by Porter in 1897. He perfused the ganglion-free apex of a dog's heart, according to a modification of the method devised in this laboratory by H. Newell Martin, and obtained an excellent series of well-sustained, long-continued, contractions; proving, thus, that in the mammalian, as well as in the cold-blooded heart nerve-cells are not essential to rhythmic activity. A number of observers have argued that the nerve-fibers, which penetrate the heart tissue everywhere, may be the source of its rhythmicity. The most prominent upholder of this view was Schiff (1850). He seems to have adopted it, after becoming convinced that nerve-cells could not be the efficient source, as the next best hypothesis. Although there is some evidence that under certain circumstances peripheral nerve-fibers may convert a constant stimulus into a rhythmic one, the belief that the rhythmicity of the heart is brought about in this way, has nothing with which to commend itself to us, as compared with the great mass of evidence favoring the myogenic theory.

Having now, I hope, succeeded in giving some idea of the rise of the theory of the heart-beat which prevails at the present time, I wish to pass to a brief discussion of the studies that have been made with regard to the influence which nerves do have upon the heart's activity; following that, and closing my paper, with some account of the work that has been done on the question of the conditions under which the heart's rhythmicity is maintained.

Mention was made in my last paper of the discovery of cardiac inhibition by the Weber brothers in 1845. Their idea of the mechanism by which it is effected, was based, it will be remembered, upon their belief in the ganglionic origin of the heart-beat. They explained cardiac inhibition simply as a special instance of the inhibitory action of a nerve upon a motor ganglion. The rise of the myogenic theory compelled the abandonment of this simple idea, and various hypotheses were proposed to account for the effects of vagus stimulation. Not the least curious of these was the one advanced by Schiff[5] (1849). This author rejected the idea of inhibition altogether. He looked upon the vagus as the true motor nerve of the heart, but believed that its ordinary function was exercised through the medium of excessively feeble stimuli. As was suggested in another connection, he thought that the constant stimulus which was carried by this nerve was transformed into a rhythmical one through some intrinsic property of the terminal nerve-fibers themselves. Since, according to his view, the usual impulse carried by the vagus is a very feeble one, it ought to be possible for strong stimulation to produce a condition of exhaustion much more promptly than in a nerve which is adapted to the transmission of strong impulses. He looked upon vagus inhibition as such a case of exhaustion from overstimulation. In support of his contention he cited the fact that weak stimulation of the trunk

[4] Gaskell, loc. cit., p. 179.

[5] Schiff, Arch. für physiol. Heilkunde, 1849, Vol. VIII.

of the vagus in the frog, frequently resulted in acceleration rather than inhibition. He likewise quoted this experiment of his own in favor of his view. He stimulated a small area of the surface of the ventricle electrically, and observed that the stimulated area remained in a relaxed condition throughout the contraction of the heart as a whole. This "local diastole" he attributed to exhaustion of the stimulated area, equivalent to that which resulted on a large scale from overstimulation of the motor nerve of the whole heart, the vagus.

We owe our most satisfactory hypothesis of the action of the vagus in terms of the myogenic theory of the heart-beat, to Gaskell.[6] This author calls attention to the fact that vagus stimulation not only slows the rate of the heart's beat, with a tendency to bring it to rest, but also diminishes the force of the individual contractions, and depresses both the excitability and the conductivity of the tissue. These facts, he says, show clearly enough that the vagus effect must be some sort of direct peripheral inhibition of the muscular tissue itself. If the action were through inhibition of some source of stimulation, the force of the beat would not be affected when the inhibitory nerve was stimulated, because, as is well known, the heart responds to stimulation according to the "all or none" law; hence weakening the stimulus could not have any effect on the force of the beat unless it became pronounced enough to stop the heart altogether. Moreover, the fact that vagus inhibition depresses both the excitability and conductivity of the tissue, is another strong indication that the action of this nerve is directly upon the muscle substance itself. The way in which the inhibition acts upon the tissue, he does not undertake to say; nor has any one offered more than the most tentative suggestions as to the mechanism of this most interesting nervous action. Gaskell has advanced other ingenious views as to the function of the vagus nerve, which the time at my disposal will not permit me to consider.

The Webers had some vague notion of what we know as cardio-acceleration. They looked upon the sympathetic nerves to the heart as possessing a function just the opposite of that exercised by the vagus, but their idea was not made the subject of rigid experimental study, so the true discovery of cardio-acceleration did not come for some years after their time. The fact that weak stimulation of the vagus often produces acceleration had been noted repeatedly, but only to create confusion in the minds of those who were trying to find a satisfactory explanation for the phenomena of inhibition. However, in 1867, v. Bezold,[7] working upon mammals, showed that stimulation of the cervical end of the cord, sectioned in the upper thoracic region, always produced pronounced acceleration under favorable circumstances, without necessarily increased blood-pressure. He had observed the increased pulse rate on stimulation of the cervical cord, some four years before, but Ludwig and Thiry pointed out that his effect might be due entirely to vasomotor changes. His last experiment excluded these by section of the cord, just below the point of stimulation; thus he was able to establish his discovery beyond question. In 1867 the brothers Cyon[8] showed that the course of the accelerator fibers must be by way of the stellate ganglion, and finally Schmiedeberg and Ludwig,[9] in 1871, traced the full course of the accelerator fibers in the dog. No more is known of the mode of action of these nerves than of the inhibitors. Gaskell points out that they exert, in general, precisely the opposite effect from that exerted by the inhibitory nerves.

The study of the conditions upon which the rhythmicity of the heart depends, began in Ludwig's laboratory, with the invention of the "frog-heart manometer" and of the means of perfusing the heart at pleasure with any desired solution. So intimately was the work of Ludwig himself associated with that of his pupils, that it is impossible to assign to each his exact part in the development of the method. Although the various publications in which the early researches along this line appear, bear as a rule the name of the pupil only, it is certainly safe to assume that the inspiration of the master's genius had much to do with the results recorded in them. As the story goes, the first perfusion apparatus was devised by E. Cyon, in the middle sixties, and consisted merely of a bowed tube, tied at one end into one of the great veins of a frog's heart, and at the other into the bulbus, and connecting by a short side branch with a small manometer. This system was filled at first with pure serum, which was pumped around and around through the heart, and the action of the organ observed by means of the manometer. This simple apparatus was quickly modified and improved, an inflow and an outflow reservoir took the place of the bowed tube, thus making the handling of the perfusing solution easier, and making it possible to control the flow of the liquid through the heart. Kronecker devised the well-known perfusion cannula, having two tubes in one in such a way that only the one tube had to be tied into the heart, and yet perfect circulation could be maintained through it. Further detailed reference to the various modifications and improvements that were made in the apparatus for studying the heart, need not be made here, because the most important of them are still in constant use in all laboratories of physiology. In spite of the argument of Kürschner against the possibility of the chemical nature of the blood having anything to do with its action upon the heart, to which I referred in my former paper, the studies of this time were wholly concerned with the chemical influence of the blood, the question as to the relative influence of its different constituents being the one which pressed for an answer. The value of certain mechanical factors, such as pressure, received due regard, but there was no doubt that the chemical structure of the blood was of paramount importance.

The problem as to the exact nature of the chemical influence of the blood upon the heart was taken up in Ludwig's labora-

[6] Gaskell, loc. cit., p. 213, et seq.

[7] v. Bezold, Untersuch. a. d. physiol. Lab. in Würzburg, 1867, Bd. II.

[8] Cyon, Arch. f. Anat., Physiol., u. wissen. Med., 1867.

[9] Schmiedeberg and Ludwig, Ber. d. k. Sächs. Gesell. d. Wissensch., Leipzig, 1870.

tory, about the year 1874, by Kronecker and Stirling,[10] and independently, in the same laboratory, by Merunowicz.[11] Curiously enough, these investigators, working side by side, came to very opposite conclusions, and, in fact, founded two opposing schools. Kronecker and Stirling observed that a frog's heart perfused with sodium chloride solution, beat with gradually diminishing force and finally came to rest; but that if it were perfused with serum, when in this exhausted condition, a prompt and long continued recovery ensued. The natural conclusion to which they came was that the washing with the saline had removed the nutrient materials of the serum, hence the heart was unable to beat until they were restored to it by fresh perfusion with serum. This experiment convinced these observers that the heart's activity depends on the presence in it of a continuous supply of nutritive proteid material. Merunowicz studied the effect of perfusing the heart with a solution of the ash of serum in place of the simple saline solution of Kronecker and Stirling. He found that the heart, perfused with this solution, did not exhibit the decline of vigor noted by those observers who worked with media containing only sodium chloride, but continued active for a long time. He noted that the ash of serum was quite alkaline, and to this feature he attributed the long continuance of the beat of the heart studied by him, and to its absence the quick decline of the heart in sodium chloride. The recovery seen by Kronecker and Stirling upon perfusion with serum was due, according to this view, merely to a renewal of the supply of alkali. It will be convenient to consider separately the development of these two schools, the one looking upon a continuous supply of proteid material as the immediate condition of rhythmic action, and the other, although not denying the ultimate dependence of the heart upon organic food stuffs, laying the greatest stress upon certain of the inorganic constituents of the blood as the intimate necessity for the beat of the heart.

In 1878 McGuire,[12] working under Kronecker's direction, added a few facts to the discussion, although they were not of overwhelming importance. He showed that serum diluted with salt solution is an excellent medium for sustaining the beat of the frog's heart, also that serum is to be preferred to either whole or laked blood. Martius,[13] in 1882, offered a really strong argument in favor of Kronecker's view. He supposed the condition of things to be as follows: the heart is to be looked upon as depending upon the presence of proteids (serum albumin) for its power to beat. The proper assimilation of the proteid by the tissue goes on, however, only in the presence of an alkali; the decline in saline solution, then, does not mean exhaustion of the supply of serum albumin, but merely the undue accumulation of acid CO_2, which interferes with the nourishment of the tissue. The revival which follows the use of the ash of serum or any other alkali, means only the restoration of the power of the tissue to assimilate. According to this idea, the tissue is not exhausted of its supply of blood proteid until it comes to rest in an alkaline salt solution. According to Kronecker's theory, the only thing which could revive the heart after this would be to supply it with serum albumin, and this Martius proved, or thought he did. He showed at any rate, that a heart after coming to rest in an alkaline medium was revived by being perfused with serum. Von Ott,[14] writing in 1883 in support of Kronecker's theory, reached some curious conclusions. It should be stated in order to make his work clear, that Gaule,[15] several years earlier, had reached the conclusion that peptones are very favorable to the heart's activity. Von Ott showed that this idea was entirely erroneous. He found, however, that after a dog was fed on this perfectly indifferent peptone, the stomach contents, even after dialysis, exerted a highly favorable influence on the heart-beat. Believing with Kronecker, that this favorable action was a sign of the presence of serum albumin, he thought that he had not only proven that serum albumin is synthesized from peptone in the alimentary tract, but that he had also obtained a most delicate method of detecting the presence of small quantities of serum albumin. He applied his test to milk and came to the conclusion that it contains this proteid, since its action on the heart is favorable. Dialysis did not diminish the action of milk any more than it had in the case of the stomach contents, so he concluded that the influence of the salts is nil in this instance also. The work of v. Ott was repeated and confirmed four years later by Frl. Popoff,[16] and a little later still by Frl. Brinck.[17] This latter investigator observed that although the ordinary forms of serum albumin have the favorable action on the heart, that prepared pure by the method of Hammarsten is without action on the organ. About this time, the Kronecker hypothesis began to be subjected to such severe criticism, and so many convincing experiments in opposition to it were being reported, that its supporters rather subsided into the background, and since 1895 only two papers of importance in support of it have appeared. The first of these was by White, in the Journal of Physiology, in 1896. This observer stated that the nutritive influence of serum albumin could be demonstrated readily enough. All that was necessary was to treat the heart with the most favorable inorganic solutions until it no longer beat in them, and then transfer it to a solution containing albumin, when, according to White, a good revival would result. As will be shown later, this result was shown by other workers not to be so conclusive as White thought it was. Göthlin,[18] quite recently (1901), has advanced some evidence in favor of the idea that a compound of paraglobulin with lecethin, such as is obtained when serum is diluted, may have some direct

[10] Kronecker and Stirling, Ludwig's Festschr., 1874, p. 173.
[11] Merunowicz, Arbeiten a. d. physiol. Anstalt zu Leipzig, 1875, p. 132.
[12] McGuire, Archiv f. Anat. u. Physiol., 1878, p. 231.
[13] Martius, ibid., 1882, p. 543.
[14] v. Ott, Archiv f. Anat. u. Physiol., 1883, p. 1.
[15] Gaule, ibid., 1878, p. 291.
[16] Popoff, ibid., 1887, p. 345.
[17] Brinck, ibid., 1887, p. 347.
[18] Göthlin, Skand. Arch. f. Physiol., 1901, p. 1.

nutritive value to the heart. His results, however, are not very positive.

We have left to consider the work of those who, with Merunowicz, looked upon the inorganic constituents of the serum as the true source of the heart's normal stimulus. The first to follow in the footsteps of this observer were Gaule[19] and Stienon,[20] both working in the same year, 1878. Both these workers emphasized the beneficial effects of alkalinity, and both believed that the heart could work at the expense of its own substance. These studies of the effect of alkalinity were soon to give place to others in which the different metallic bases of the serum were to become the subjects of investigation. The impulse to this work was given by the English physician, Sidney Ringer,[21] and to him, also, belongs a considerable portion of the credit for developing the subject to its present standpoint. In Ringer's first experiments on this point he made up a solution of sodium chloride in ordinary hydrant water, and observed that it had a tendency to throw the heart into a condition of tonic contraction. He found that this contraction could be overcome by the addition of a small proportion of potassium chloride to the solution. He found that this mixture of sodium and potassium chlorides in solution was very favorable to the heart's activity. His account of this set of experiments appeared in the Journal of Physiology in 1880. His attention was soon, however, directed to the fact that he had not used sufficient care in making up his solutions. He then examined the water with which his solutions had been made up, and found that it contained a considerable proportion of calcium salts in solution. This discovery obliged him to repeat his former work, which he did with the well-known result that he demonstrated the action of calcium to produce tonic shortening in the tissue, and also proposed as a good solution for use in irrigating hearts, the one containing calcium, sodium, and potassium salts, which has since been known by his name. It was quickly shown by Ringer and others that hearts perfused with his solution continued active fully as long as in the best experiments with serum perfusion. This result made it clear that if the heart has any immediate dependence upon the serum content of the blood, that dependence is by no means so apparent as its salt requirement is. The problem, at this point, assumed a twofold nature. The mode of interaction of the salts of the serum was to be studied, and it was to be definitely determined whether or not any organic substances are immediately essential to the heart's activity in the sense in which the salts are. These studies were prosecuted with vigor both in England and in this country.

A number of papers have appeared from time to time in which the attempt has been made to prove that one or the other organic substance added to a Ringer's solution, improved it as a sustaining medium for the cold-blooded heart. Ringer himself thought that small additions of blood, serum, milk, or whey kept his hearts in activity longer than his inorganic solution alone. He was careful to point out, however, that the presence of the salts was the prime requisite for maintaining rhythmicity. He pointed out incidentally in this connection, that dialysis of blood or milk does not rid them of their calcium content, hence the favorable result of v. Ott with these substances was to be explained as due to the calcium which remained in them after dialysis. Heffter,[23] in 1892, and a year later Albanese,[24] concluded that viscosity was an essential feature of a satisfactory nutritive solution. They therefore recommended gum-arabic as a good substance to be included in the solution. As a matter of fact, the addition of this gum to saline solution improved it as a nutritive medium, but as Howell pointed out, this is due to the fact that gum-arabic is a calcium compound, rather than to any physical property it possesses. Locke,[25] in 1895, although denying the usefulness of gum-arabic, thought that some organic substance would be beneficial, and came to the conclusion that dextrose is such a substance.

Howell's first paper upon this subject, in 1893, took the opposite ground. In collaboration with Miss Cooke,[26] he undertook to make a comparative study of the nutritive value of the different blood-proteids, by determining their relative influence in prolonging the beat of the heart when perfused with nutritive solutions. These authors found, however, that addition of either of the blood-proteids had no measurable effect in prolonging the activity of the heart. They tried to get at the question in another way, by determining quantitively how much proteid was used up by the heart in the course of a long perfusion, but were unable to demonstrate any disappearance of proteid under these conditions. This paper also disposed effectually of v. Ott's idea that serum albumin is synthesized from peptone in the digestive tract, by showing that the beneficial effect of stomach contents is due to the salts, especially of calcium, contained in them. Eaton,[27] at this same time, showed the importance of calcium in another way. He found that if the calcium were precipitated out of the solution by the addition of a little sodium oxalate, its great value as a nutritive medium was lost, but that it returned again with the addition of an excess of a calcium salt. As furnishing practically final proof of the predominant importance of the salts in sustaining the rhythmic action of the heart, the papers of Howell[27] and Greene[28] in 1898 should be quoted. The observations recorded in these papers were made upon the terrapin. It had been supposed by those who favored the view of Kronecker, that enough serum remained in the spongy cavities of the heart to account for the long-continued

[19] Gaule, loc. cit.

[20] Stienon, Archiv f. Anat. u. Physiol., 1878, p. 263.

[21] For the papers of Ringer see the Jour. of Physiol. from Vol. III to Vol XIV.

[23] Heffter, Arch. f. exp. Path. u. Pharm., 1892, p. 41.

[24] Albanese, ibid., 1893, p. 297.

[25] Locke, Jour. of Physiol., 1895, p. 332.

[26] Howell and Cooke, ibid., 1893, p. 198.

[27] Eaton, foot-note to Howell and Cooke, loc. cit.

[27] Howell, Amer. Jour. of Physiol., 1898, Vol. II, p. 47.

[28] Greene, ibid., 1898, p. 82.

activity so frequently observed in inorganic solutions. The work of Howell and Greene was to test this point. Howell showed that the venous portion of the heart, although entirely without any thickness of tissue or spongy structure, conducted itself in inorganic solutions very much as does the heavier ventricle. Long and well-sustained series were obtained from venous strips without the employment of any organic substance whatever, save that contained within the tissue. Greene demonstrated that the ventricle could not require a constant supply of serum albumin by calculating the amount of it which would be used up in doing the amount of work performed by a heart on an inorganic diet, and showing that more would be required than could be supposed, on the most liberal estimate, to lurk in the cavities of the heart, after the thorough washing out to which it was subjected. Finally Walden[29] showed that the experiment of White, in which he revived a heart by serum after it ceased to beat in Ringer's fluid, could be reversed. A heart that would no longer beat in serum could be revived by perfusion with inorganic Ringer's solution.

At the present time the ability of the heart to continue active for a very long time on a purely inorganic diet is generally conceded. The question as to the relative importance of the different constituents of Ringer's solution, in maintaining the beat of the heart, is now the subject of much discussion and a great deal of experimental study. Any consideration of this question would be out of place in a purely historical presentation such as this aims to be.

[29] Walden, Amer. Jour. of Physiol., Vol. III, p. 123.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

October 9, 1905.

Dr. W. G. MacCallum was elected president for the coming year and Dr. C. H. Bunting was elected secretary.

Bilateral Exostoses on the Inferior Surface of the Calcaneus, Gonorrhœal in Origin (Pododynia Gonorrhoica). DR. BARKER.

This man, twenty-nine years old, a weaver by trade, entered the hospital complaining of inability to work, owing to soreness in the lower extremities. Up to two years ago he enjoyed fairly good health, with the exception of the ordinary diseases of childhood, and of a malarial attack at the age of fifteen. About two years ago, while at work, he was suddenly seized with a sharp pain in the lower part of the abdomen; it radiated to the end of the penis, but as far as the patient can remember, did not run down the thighs or into the back. At about this time he passed bloody urine occasionally and was so ill that he was prevented from working. He denies venereal infection, but the attack just mentioned may have been due to gonorrhœa. Shortly after this attack the patient began to have soreness in the bottom of his feet. This soreness extended, he says, into the legs and thighs, and finally affected the back. Two months after the onset of the soreness he gave up his work for eight weeks, but returned to it again and worked until nine months ago, when the trouble became so serious that he was compelled to desist. Some eighteen months ago he had a very severe attack of "sore eyes," and three months ago one of his eyes was again much inflamed. Ophthalmoscopic examination by Dr. Randolph since entrance to the hospital reveals a previous iritis of severe grade in both eyes.

On examination the patient is seen to be rather a spare man, under-nourished. He stands and walks with great difficulty, owing to pain, especially in the back part of each foot. The peculiarity of his gait is due to his effort to keep the pressure off the painful part of the feet. The lower extremities are somewhat atrophied, but probably not more than the disuse accounts for. The examination of sensation reveals no abnormalities. The motor power is nowhere involved. The deep reflexes are, however, markedly increased, especially in the lower extremities; the knee-kicks are very active, and a slight patellar clonus can sometimes be obtained on the left side. The Babinski phenomenon cannot be elicited, nor is Oppenheim's sign present. The mechanical excitability of the muscles is increased, and there is marked dermatographia.

No sufficient evidence of organic disease of the nervous system has as yet been found in the case. There is marked tenderness on pressure on the plantar surface of the foot near the heel on each side. Dr. Cole suggested the possibility of gonorrhœal exostoses, such as have been found in the cases which Dr. Baer has been studying of late. Dr. Thomas, who saw the case also with especial reference to the nervous symptoms, favored this diagnosis. The patient was accordingly sent to the X-ray room, and the negatives which I now pass around were made by Dr. Baetjer. They leave no doubt as to the condition. An exostosis is easily visible on the calcaneus of each foot. It has the typical "worm-eaten" appearance, so often found in these cases; the appearance, Dr. Baetjer informs me, is that of gonorrhœal rather than of syphilitic bony growth.

I should like to draw the attention of the society to the exact position of the exostoses in this patient. It will be noted that the new growth is situated, not on the tuber calcanei, but in front of it, and the exostosis is not connected with either the medial or lateral process of the tuber. On the contrary it projects from the prismatic body (corpus calcanei) of the heel bone. In this position it can scarcely have anything to do with the attachment of the aponeurosis plantaris, which is situated more posteriorly. The exostosis lies more

nearly in the position of the attachment of the posterior extremity of the ligamentum plantare longum, or possibly in the region of origin of the M. abductor digiti quinti on the inferior surface of the calcaneus. Nor can the exostosis, in this case at any rate, be connected with a bursa, inasmuch as the only bursa occurring in this part of the foot is the bursa subcutanea calcanea, which lies just beneath the skin on the inferior surface of the tuber calcanei. I mention this point inasmuch as I understand that in some of Dr. Baer's cases and in other cases which have been reported, the exostoses correspond more nearly to the attachment of the aponeurosis plantaris; a relation to the bursa has also been postulated in certain instances.

We shall refer this patient to Dr. Baer for removal of the exostoses, after which we shall expect him to regain his health.

The increased reflexes and increased mechanical excitability of the muscles are in all probability neurasthenic symptoms which will disappear under suitable treatment.

Dr. Baer, in discussion, told of six cases from his clinic in the last three years, from two of which he got gonococcus in pure culture and from two the stained organism in section. One case was not operated on, and one showed no organisms. These cases were all bilateral, in males, and within one year after urethritis.

Perichondritis, Probably of Gonorrhœal Origin. DR. BARKER.

The patient, a Polish cigarmaker, twenty-seven years old, was admitted to Ward F on September 29, 1905, complaining of rheumatism, and of swelling in the neck. He had applied on August 31 to the genito-urinary dispensary for treatment of an acute urethritis contracted a few days earlier. Gonococci were at that time present in the urethral discharge. On September 18 he began to have pain in the right shoulder and in the right hip. The shoulder became hot, tender, and swollen, and for four days he was unable to put on his coat. Pain then appeared in the right knee, and since that time the metacarpophalangeal joints of the left hand, the metatarsophalangeal joints of the right foot, the left knee and the right ankle have all been painful.

Four days before the present admission the patient noted swelling of his Adam's apple and felt pain, which radiated down the wind-pipe. He had some difficulty in swallowing, but no difficulty in respiration, nor was there any change in his voice. He has complained also of slight stiffness in his right jaw-bone. There has been but little effusion in the joints, with the exception, possibly, of the right shoulder joint at the onset of the attack. The blood presents a moderate grade of secondary anæmia. There are still a few pus-cells in the urine, but otherwise the urine is negative. Dr. Warfield has made a laryngoscopic examination, and finds nothing abnormal inside the larynx. There is no enlargement of the tonsils.

Palpation of the larynx reveals tenderness and slight swelling on the upper margin of the right lamina of the thyreoid cartilage, a little in front of the superior thyreoid tubercle. There has also been tenderness over the right side of the cricoid cartilage, and at present the patient complains when the cartilages of the trachea are pressed upon. There is no superficial redness. The hyoid bone is not tender. No changes can be made out in the thyreoid gland. Otherwise the examination is negative.

The occurrence of perichondritis following gonorrhœa is of interest. Coming on in close association with gonorrhœal arthritis it seems very probable that this perichondritis is gonorrhœal in origin, though the absolute proof (demonstration of gonococci in the lesion) is wanting. Dr. Cole, who has recently been reviewing the literature of the complications and sequelæ of gonorrhœa in connection with the material which has come under observation in the hospital, does not recall having met with reported cases of perichondritis, but there seems to be no reason why the complication should not occur.[1]

Bronzed Diabetes, with Enlargement of the Liver and Palpable Spleen. DR. BARKER.

The patient, J. W. S., a bricklayer, 53 years old, was admitted to Ward F on October 6, 1905, complaining of weakness and great thirst. He suffered from an attack of pneumonia in his seventeenth year. Chronic constipation has existed; otherwise he has been healthy and his habits have been good. His average weight is 160 pounds. We have inquired carefully, but can, in connection with the present illness, get no history of symptoms noticed by the patient dating farther back than three months. At about that time the patient noticed that he was growing weak in the legs. Six weeks ago he observed that he was passing large quantities of urine, urinating eight or ten times during the day, and three or four times during the night. The polyuria has been accompanied by excessive thirst and a voracious appetite, especially for sweets. During the past four weeks the patient has lost strength rapidly, and he states that he has diminished in weight by twenty pounds during the same period. He stopped work a week before admission.

The bronzing of the skin is, as you see, pronounced, especially on those parts of the body which have been exposed, though bronzing of a less degree affects the skin of the whole body. On the thorax the bronzing is mottled by small, paler areas, about 6 to 8 mm. in diameter. The openings of the sebaceous glands are very prominent. The patient states that he has always been of dark complexion, and he has not noticed that his skin is darker now than it was a year ago. Members

[1] Since the meeting at which this case was shown Dr. Sylvan Rosenheim has called my attention to three references bearing upon involvement of the larynx in gonorrhœa. These are all in Friedrich's Rhinology, Laryngology, and Otology in General Medicine. In two of the cases there were redness, swelling and fluctuation over the arytenoid cartilage, with loss of adduction of the vocal cord and aphonia; violent pain in the region of the larynx was complained of and was increased by pressure on the thyreoid cartilage. The third case referred to was one of bilateral paralysis of the M. crico-arytenoideus posterior, supposedly due to a neuritis of gonorrhœal origin.

of his family, however, state that they have noticed the increased darkening of the skin.

The patient is not anæmic. He has a normal number of white and red corpuscles, and 95 per cent of hæmoglobin in his blood. The urine shows a specific gravity of from 1034 to 1037. It is free from albumin, but contains a large quantity of sugar. An examination of a single specimen on entrance revealed the presence of 11.45 per cent of glucose. During the past twenty-four hours the patient has excreted 96.6 grams of glucose, an amount corresponding to 6.4 per cent of the urine. Acetone and diacetic acid are present in the urinary secretion to-day.

The patient's liver is very much enlarged, the superficial dulness extending in the right mammillary line from the sixth rib to a point 12.5 cm. below the costal margin. On palpation it is felt to be hard, and the surface is smooth. The enlargement involves the whole organ, including the left lobe. The edge of the spleen can be felt on deep inspiration in the left hypochondrium. In addition to the pigmentation there are extensive reddened areas of the skin on those parts of the body especially exposed to mechanical irritation; namely, in and about the axilla, above the breasts, at the waist band and between the thighs. This redness is in part a traumatic erythema, in part actually an eczema. Examination of the other organs is negative. The knee-jerks are present on both sides.

To-day Dr. Walter Jones, in the laboratory of physiological chemistry, made a spectroscopic examination of the fresh blood, but found only the normal bands of oxyhæmoglobin. The coagulation time is three and a quarter minutes. Blood pressure, 115 millimeters of mercury.

Regarding the diagnosis, it seems clear that we have to deal with a case of bronzed diabetes in association with hæmochromatosis, hypertrophic cirrhosis of the liver, and enlargement of the spleen. Doubtless chronic interstitial pancreatitis with enlargement also exists. The condition is an interesting one, and this is, I believe, the fifth instance met with in this hospital. Dr. Osler has reported several of the earlier cases.

It will be recalled that Dr. Opie some years ago showed the relation which exists between the so-called hæmochromatosis of von Recklinghausen, and the *diabète bronzé* of Hanot and Chauffard. It seems probable, from the studies of Opie, P. Marie, Anschütz, Buss, and others, that the diabetes is secondary to the hæmochromatosis. The conception of the disease held at present is as follows: For some reason as yet unknown two kinds of pigment accumulate in the body, the so-called hæmosiderin in the epithelial cells of the liver, pancreas and other glands, and the so-called hæmofuscin, in the smooth muscle of the alimentary tract, of the blood-vessels, of the genito-urinary tract, etc. As a result of the deposition of the hæmosiderin in the liver and pancreas the parenchymatous cells of these organs degenerate. This degeneration, together with the direct irritation of the pigment itself, acts as a stimulus to the growth of connective-tissue, and hypertrophic cirrhosis of the liver and chronic interstitial pancreatitis develop, the pancreas as a rule becoming half again as large as normal. When the chronic interstitial pancreatitis has reached a certain grade (according to Opie, when it has destroyed a sufficient number of the islands of Langerhans) diabetes develops. The diabetes is therefore a terminal phenomenon, and cases have been as a rule rapidly fatal after the diabetic symptoms have appeared. The hæmochromatosis, however, together with enlargement of the liver, may exist for many years without development of diabetes, and the case recorded by Dr. Opie never developed glycosuria. His patient died of typhoid fever.

In the ward rounds we have discussed in this case the possibilities of pathogenesis, with the hope of getting some clue which might enable us to reproduce the disease experimentally in animals, but the etiology and pathogenesis are far from clear.

In some instances of hæmochromatosis hæmorrhages into the peritoneal cavity or into the pleura or into the pericardium have existed, but these are not always present, and no evidence of such hæmorrhages can be found in the present case. Nor is there any evidence of increased blood destruction; the patient is not, nor has he been, anæmic. The accumulation of hæmosiderin,[2] assuming that it is derived from disintegrating red blood corpuscles, might occur conceivably from either one or two causes. Its accumulation might on the one hand be due to some abnormal cleavage of blood pigment. We know from laboratory studies that hæmoglobin may break up in different ways. It is possible that, in disease, cleavage may follow some route other than that normally travelled. On the other hand, it is possible that changes take place in the cells of the body, especially in the liver, which prevent the normal metabolism of the breaking down blood pigment, so that, though hæmoglobin cleavage may be regular as far as it goes, the cells may be unable to carry on the processes by which the cleavage products are normally utilized. It seems probable that some deep-lying disturbance of the iron metabolism is at the bottom of the affection, for the studies of Anschütz show that in this disease no less than 55 per cent of the ash of the liver consists of iron, an amount which is at least 100 times as great as the normal percentage.

Inversion of Uterus. DR. WILLIAMS.

CASE 1.—Woman, 24 years old; married two years; miscarriage at sixth month fifteen months before. In this instance patient went to term; labor was normal through first and second stages. The Credé method being ineffectual in removing the placenta, it was removed manually. The patient was very much shocked, but there was no hemorrhage. Twenty-four hours later Dr. Williams found her radials pulseless, heart rate 168, and the patient bathed in sweat. Palpation disclosed a firm hard mass in abdomen, and on vaginal examination the pelvic cavity was found filled with a large

[2] Unfortunately, "hæmosiderin" is as yet a mere histological term; it may or may not be a single chemical substance; it should be more thoroughly studied.

round mass with ragged edges. Above the tumor mass was the firm hard cervical ring through which the uterus had inverted. The ring was dilated manually, and the uterus being reverted promptly retracted and forced the hand out. The patient's condition improved rapidly, pulse was 100, and she was out of danger in a few hours.

CASE 2.—Girl, 21 years of age; primipara delivered by forceps and placenta removed manually. When seen in consultation on the third day, her pulse was 140 and her uterus inverted, the cervix was hard, about the size of a dollar, and tightly gripped the inverted uterus. There was marked pressure on the bladder, which was greatly distended with bloody urine. Being unable to dilate the hard cervix, laparotomy was done, the cervix incised and with fingers in the vagina the uterus was reverted, the patient making a satisfactory recovery. Inversions of the uterus mostly occur in primiparæ attended by ignorant midwives, and are caused by traction on the cord or by too great pressure on the uterus from above.

Thoracic Aneurisms. DR. BAETJER.

The X-ray has proven most useful in diagnosing conditions and diseases of the chest. We can now practically make positive and negative diagnoses. Both the radiographic and fluoroscopic methods are used in examination. The routine in this hospital is to make a physical examination, first to see that there are no abnormalities, then place the tube on a level with the third rib twenty-four inches from the patient's back and examine the chest from the front. The patient is turned around and examined in the same way from the back, and then sidewise by transverse illumination. In this way we cannot only get location of the aneurism but we can see whether or not it is pedicled. The normal fluorescent screen reveals the dark line of the spine and sternum about two inches wide, the shadows of the pulsating heart, and of the diaphragm. Any shadow to the right or left of the sternum is abnormal and may be due to enlarged glands, new growth, or aneurism. The shadow of a new growth is darker and more hazy than the shadow of the aneurism. Dilatation of the aorta is positive; when in pulsation the aorta disappears behind the sternum. To make a diagnosis of aneurism the shadow must persist between pulsations.

NOTES ON NEW BOOKS.

The Principles and Practice of Gynecology. By E. C. DUDLEY, A. M., M. D., Professor of Gynecology, Northwestern University Medical School. Fourth edition revised. (*Philadelphia: Lea Brothers & Co., 1904.*)

This edition is considerably larger than its predecessors. The introductory chapters give the reader a good idea of the normal functions of the pelvic organs and clearly outline the usual method of making pelvic examinations. The chapters on technique are detailed and explicit, and the section devoted to the preparatory and after treatment of patients is excellent.

The book is essentially a mirror of the methods employed by Dr. Dudley in his own clinic and little space is accorded the operations of other surgeons. This certainly increases the individuality of the work. The book is clearly written, the illustrations are good, and the type perfectly satisfactory. Taken as a whole the book is a safe clinical guide, notwithstanding the fact that its pathology is rather hazy and leaves much to be desired.

Addresses and Other Papers. By WILLIAM WILLIAMS KEEN, M. D., LL. D., F. R. C. S. (Hon.), Professor of Surgery, Jefferson Medical College, etc. (*Philadelphia and London: W. B. Saunders & Company, 1905.*)

This volume of addresses offers a wide range of subjects presented in a pleasing and interesting way. The historical and reminiscential papers seem upon the whole the most happy in matter and arrangement. They indicate a careful study of original sources of information and often, in fact, furnish history at first hand from the author's own experience. A good example may be found in the "History of the Philadelphia School of Anatomy and its Relation to Medical Teaching," with its charming personal sketches of Lawrance, Godman, Webster, Pancoast, Agnew, Da Costa, Brinton, and many others. The paper is enlivened by many touches of humor and several lively tales of early events in this pioneer school of anatomy. Another paper in the same vein and equally interesting is entitled "Surgical Reminiscences of the Civil War." We know of no more vivid picture of the surgical aspects of that memorable conflict. The deficiences and crudities of the medical and surgical service, the unpreparedness of the Army Medical Corps for the emergencies which had been thrust upon it, the lack of experience of many surgeons, the sufferings of the wounded, and the frightful mortality from surgical accidents, which we now know to be preventable, are graphically told.

Among the most exclusively professional papers may be mentioned "The Debt of the Public to the Medical Profession," "The Progress of Surgery in the Nineteenth Century," and "Medicine as a Career for Educated Men." These display high ideals of medicine and lofty hopes for its future, presented in a forceful and impressive manner.

In another vein may be mentioned a brief paper on the "Cheerfulness of Death," indicating a depth of religious feeling on the part of the author and a habit of mind, which are not common among medical men. The whole book is upon a high plane of thought and should have a wide circulation.

A Text-Book of Obstetrics. By ADAM H. WRIGHT, M. D., Professor of Obstetrics, University of Toronto. (*New York and London: D. Appleton and Company, 1905.*)

Dr. Wright is to be congratulated on the excellence of his book, which, apart from the first few sections dealing with anatomy and physiology, leaves little to be desired in the treatment of the subject; the author's apology in his preface is scarcely sufficient to excuse the brevity and lack of detail in this portion of the book.

The sections dealing with the management of pregnancy and labor are excellent, and it is interesting to note the importance laid upon pelvimetry. The section on the mechanism of labor is very brief. Probably the most interesting section in the book is that dealing with the intercurrent diseases of pregnancy. It is here that one gets an idea of the very wide extent of Dr. Wright's experience and his great capacity for clinical observation. In the section on eclampsia wise advise is given against the employment of useless drugs, but the treatment is not in accord with the usually accepted ideas. Indeed, here is one of the most

marked inconsistencies in the book, for, while immediate delivery of the patient, which offers the only possible chance of life for the child, is not considered advisable on account of the danger to the mother, in the treatment of postpartum hemorrhage, on the other hand, an expectant policy is advised on account of the child, even though the danger to the mother is considerably greater than it would be in eclampsia. The treatment of occipito-posterior positions is taken up somewhat extensively. The treatment advised is that in general use in the best maternities. Transverse presentations are rather scantily treated, and in the treatment of prolapsed cord the forceps is placed next to attempts at reposition, rather than version which would appear to give a better chance for the child. The sections on puerperal infection are full and complete. The treatment advised—purgation, water in large quantities, and stimulation, together with antistreptococcus serum—is most judicious. The sections on obstetrical operations are very complete. Dr. Wright believes in the waiting treatment rather than the immediate repair of extensive perineal tears. In the application of forceps he himself believes in the cephalic application, but he has described the pelvic application, which is the method in common use in England and in Canada.

The introduction of clinical histories of interesting cases, together with the forceful and personal style of Dr. Wright's diction, makes the book extremely interesting reading, and the excellent print and general get-up of the book commend it to the medical student as one of the most valuable of the numerous text-books on obstetrics which have recently appeared.

The Pharmacopœia of the United States of America. Eighth decennial revision. By authority of the United States Pharmacopœial Convention held at Washington, A. D. 1900. Revised by the Committee of Revision and published by the Board of Trustees. Official from September 1, 1905. (*Philadelphia: P. Blakiston's Son & Company.*)

At last the long expected new Pharmacopœia has been issued, and will be official from September 1, 1905. The former edition was known as the 1890 revision; the new work will be officially designated as the eighth decennial revision, the date 1900 forming no part of the title.

In the new book there are more important changes made in the strength of the preparations, more new products added, and more drugs standardized than ever before. Many synthetic articles, such as Trional and Urotropin have been admitted, but not under these names. It will almost be necessary for the physician to carry a pocket edition, for reference, when he wishes to prescribe these remedies by their pharmacopœial name. For instance: Trional is admitted as Sulphonethylmethane, Phenacetin as Acetophenitidin, Urotropin as Cystogen; and the many other names given the combination of formaldehyde and ammonia, as Hexamethylenamine.

J. L. W.

THE JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice, abstracts of papers read, and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly.

Volume XVI is nearly completed. The subscription price is $2.00 per year. The set of sixteen volumes will be sold for $7.00.

PAPERS ON TYPHOID FEVERS.

(From Volume VIII of the Johns Hopkins Hospital Reports.)

On the Surgical Treatment of Perforating Typhoid Ulcer. By J. M. T. Finney, M. D.

Laparotomy for Intestinal Perforation in Typhoid Fever. By Harvey W. Cushing, M. D.

Unusual Forms of Infection with the Typhoid Bacillus, with Especial Reference to Typhoid Fever without Intestinal Lesions. By Simon Flexner, M. D.

Coincident Typhoid and Malarial Infection. By Irving Phillips Lyon, M. D.

On the Oesophageal Complications of Typhoid Fever. By James F. Mitchell, M. D.

On Hæmorrhagic Typhoid Fever. By Louis P. Hamburger, M. D.

Puerperal Infection with the Bacillus Typhosus. By George W. Dobbin, M. D.

Gall-Bladder Complications of Typhoid Fever. By C. N. B. Camac, M. D.

Hemiplegia in Typhoid Fever. By William Osler, M. D.

Hepatic Complications of Typhoid Fever. By William Osler, M. D.

Study of the Widal Reaction in 265 Cases of Typhoid Fever. By Norman B. Gwyn, M. B.

Note on the Disinfection of Infected Typhoid Urines. By Norman B. Gwyn, M. B.

A Case of Typhoid Fever with Early Oculo-Motor Paresis of Left Eye. By Chas. P. Emerson, M. D.

Chronic Cystitis Due to the Typhoid Bacillus. By Hugh H. Young, M. D.

Summary of Cases of Typhoid Fever, 1889-1899. By William Osler, M. D.

Special Features and Complications of Cases of Typhoid Fever. By William Osler, M. D.

Observations on the Blood in Typhoid Fever. By William Sydney Thayer, M. D.

Price, bound in paper, $3.00. Orders should be addressed to

The Johns Hopkins Press,

Baltimore, Md.

SEPARATE MONOGRAPHS REPRINTED FROM THE JOHNS HOPKINS HOSPITAL REPORTS.

Studies in Dermatology. By T. C. Gilchrist, M. D., and Emmet Rixford, M. D. 1 volume of 164 pages and 41 full-page plates. Price, bound in paper, $3.00.

The Malarial Fevers of Baltimore. By W. S. Thayer, M. D., and J. Hewetson, M. D. **And A Study of some Fatal Cases of Malaria.** By Lewellys F. Barker, M. B. 1 volume of 280 pages. Price, bound in paper, $2.75.

Pathology of Toxalbumin Intoxications. By Simon Flexner, M. D. 1 volume of 150 pages with 4 full-page lithographs. Price, in paper, $2.00.

Studies in Typhoid Fever. I, II, III. By William Osler, M. D., and others. Extracted from Vols. IV, V and VIII of the Johns Hopkins Hospital Reports. 1 volume of 881 pages. Price, bound in cloth, $5.00.

Orders should be addressed to

The Johns Hopkins Press, Baltimore, Md.

The Johns Hopkins Hospital Bulletins are issued monthly. They are printed by the FRIEDENWALD CO., Baltimore. Single copies may be procured from NUNN & CO. and the BALTIMORE NEWS CO., Baltimore. Subscriptions, $2.00 a year, may be addressed to the publishers, THE JOHNS HOPKINS PRESS, BALTIMORE; single copies will be sent by mail for twenty-five cents each.